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*APPLICATION NUMBER:*  
**206538Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Established Name insulin glargine [rDNA origin]  
injection, 300 Units/mL  
(Proposed) Trade Name Toujeo®  
Therapeutic Class insulin  
Applicant Sanofi-Aventis U.S. LLC

Formulation(s) Subcutaneous injection  
Dosing Regimen Once daily  
Indication(s) To improve glycemic control in  
adults with diabetes mellitus.  
Intended Population(s) Adults with diabetes mellitus

## TABLE OF CONTENTS

<b>1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>14</b>
1.1 Recommendation on Regulatory Action .....	14
1.2 Risk Benefit Assessment.....	14
1.3 Recommendations for Postmarket Risk Management Activities .....	16
1.4 Recommendations for Postmarket Studies/Clinical Trials.....	16
<b>2 INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>16</b>
2.1 Product Information .....	16
2.2 Tables of Currently Available Treatments for Proposed Indications .....	17
2.3 Availability of Proposed Active Ingredient in the United States .....	18
2.4 Important Safety Issues With Consideration to Related Drugs.....	18
2.5 Summary of Presubmission Regulatory Activity Related to Submission .....	18
2.6 Other Relevant Background Information.....	24
<b>3 ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>24</b>
3.1 Submission Quality and Integrity .....	24
3.2 Compliance with Good Clinical Practices .....	24
3.3 Financial Disclosures .....	25
<b>4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>25</b>
4.1 Chemistry Manufacturing and Controls .....	25
4.2 Clinical Microbiology .....	26
4.3 Preclinical Pharmacology/Toxicology .....	26
4.4 Clinical Pharmacology .....	26
4.4.1 Mechanism of Action .....	27
4.4.2 Pharmacodynamics .....	27
4.4.3 Pharmacokinetics .....	30
<b>5 SOURCES OF CLINICAL DATA.....</b>	<b>30</b>
5.1 Tables of Studies/Clinical Trials.....	30
5.2 Review Strategy .....	35
5.3 Discussion of Individual Studies/Clinical Trials.....	36
Common elements among 4 pivotal studies .....	36
Review of individual pivotal trials.....	43
<b>6 REVIEW OF EFFICACY .....</b>	<b>59</b>
Efficacy Summary .....	59
..... (b) (4) .....	62
6.1 Indication .....	62
6.1.1 Methods.....	63
6.1.2 Demographics .....	63
6.1.3 Subject Disposition .....	76
6.1.4 Analysis of Primary Endpoint(s).....	81
6.1.4.1.1 Primary efficacy endpoint - EFC12456 - T1DM.....	82
6.1.4.1.2 Secondary efficacy endpoints - EFC12456 – T1DM .....	86
6.1.4.1.3 Other Endpoints - EFC12456 – T1DM .....	88
6.1.4.1.4 Subpopulations - EFC12456 – T1DM.....	91
6.1.4.2.1 Primary efficacy endpoint - EFC11628 – T2DM patients taking IMP plus meal time insulin .....	92
6.1.4.2.2 Secondary efficacy endpoints - EFC11628 – T2DM .....	96
6.1.4.2.3 Other Endpoints - EFC11628 – T2DM .....	98

6.1.4.2.4 Subpopulations - EFC11628 –T2DM.....	101
6.1.4.3.1 Primary efficacy endpoint - EFC11629 - T2DM patients taking oral antihyperglycemic drugs(s) (OADs).....	102
6.1.4.3.2 Secondary endpoints - EFC11629 - T2DM.....	106
6.1.4.3.3 Other endpoints - EFC11629 - T2DM .....	109
6.1.4.3.4 Subpopulations - EFC11629- T2DM .....	112
6.1.4.4.1 Primary efficacy endpoint - EFC12347 –T2DM insulin naive .....	113
6.1.4.4.2 Secondary endpoints - EFC12347- T2DM.....	118
6.1.4.4.3 Other endpoints - EFC12347 – T2DM.....	121
6.1.4.4.4 Subpopulations - EFC12347 - T2DM .....	123
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.....	124
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects .....	125
6.1.10 Additional Efficacy Issues/Analyses.....	125
<b>7 REVIEW OF SAFETY .....</b>	<b>125</b>
Safety Summary.....	125
7.1 Methods .....	126
7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	126
7.1.2 Categorization of Adverse Events .....	127
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence .....	129
7.2 Adequacy of Safety Assessments .....	129
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	129
7.2.2 Explorations for Dose Response .....	135
7.2.3 Special Animal and/or In Vitro Testing .....	135
7.2.4 Routine Clinical Testing .....	135
7.2.5 Metabolic, Clearance, and Interaction Workup.....	135
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	135
7.3 Major Safety Results.....	136
7.3.1 Deaths .....	136
7.3.2 Nonfatal Serious Adverse Events.....	143
7.3.3 Dropouts and/or Discontinuations.....	150
7.3.4 Significant Adverse Events .....	154
7.3.5 Submission Specific Primary Safety Concerns .....	172
7.4 Supportive Safety Results .....	184
7.4.1 Common Adverse Events.....	184
7.4.2 Laboratory Findings .....	193
7.4.3 Vital Signs.....	195
7.4.4 Electrocardiograms (ECGs) .....	195
7.4.5 Special Safety Studies/Clinical Trials .....	195
7.4.6 Immunogenicity .....	215
7.5 Other Safety Explorations.....	220
7.5.1 Dose Dependency for Adverse Events for switching from HOE901-U300 to other insulins .....	220
7.5.2 Time Dependency for Adverse Events.....	228
7.5.3 Drug-Demographic Interactions.....	228
7.5.4 Drug-Disease Interactions .....	229
7.5.5 Drug-Drug Interactions .....	229
7.6 Additional Safety Evaluations .....	229
7.6.1 Human Carcinogenicity .....	229
7.6.2 Human Reproduction and Pregnancy Data .....	229
7.6.3 Pediatrics and Assessment of Effects on Growth.....	230
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound .....	231
7.7 Additional Submissions: .....	231
<b>8 POSTMARKET EXPERIENCE.....</b>	<b>231</b>

<b>9 APPENDICES.....</b>	<b>231</b>
9.1 Literature Review/References.....	231
9.2 Labeling Recommendations.....	231
9.3 Advisory Committee Meeting.....	231
9.4 Clinical Investigator Financial Disclosure Review Template.....	232

## Table of Tables

Table 1 – Comparison of PD effect at steady state of U300 vs. U100 glargine .....	27
Table 2 - Table of four pivotal trials and two substudies supporting the clinical efficacy and safety evaluation for this NDA .....	32
Table 3 - Phase 2 study, PDY12777 (supporting safety assessment only) .....	33
Table 4 – Other clinical studies performed by the Sponsor (not supporting the efficacy and safety review for this NDA, including Clinical Pharmacology studies) .....	33
Table 5 - Common characteristics among all pivotal studies (EFC12456, EFC11628, EFC11629, and EFC12347) .....	36
Table 6 - Methodology of starting IMP dose among pivotal trials (EFC12456, EFC11628, EFC11629, and EFC12347).....	39
Table 7 - Pen characteristics used in pivotal trials.....	40
Table 8 - Titration of basal insulin used in pivotal trials (EFC12456, EFC11628, EFC11629, and EFC12347).....	41
Table 9 – Prior and concomitant antidiabetic medications .....	41
Table 10 - Analysis windows definition .....	47
Table 11 – Summary statistics for HbA1c results across pivotal trials .....	60
Table 12 – Difference in insulin doses (mean U and mean U/kg) between baseline and month 6 across 4 pivotal trials .....	61
Table 13 - EFC12456 - Subject demographics and baseline characteristics .....	64
Table 14 - EFC11628 - Subject demographics and baseline characteristics .....	67
Table 15 – EFC11629 – Subject demographics and baseline characteristics .....	71
Table 16 – EFC11629 - Antidiabetic medications taken by the patients in the 3 months before screening up to the first injection of IMP .....	73
Table 17 - EFC12347 - Subject demographics and baseline characteristics .....	74
Table 18 - EFC12347 - Summary of disease characteristics at baseline - randomized population .....	75
Table 19 - EFC12456 – Patient disposition - randomized population.....	76
Table 20 – EFC11628 - Patient disposition - randomized population.....	78
Table 21 - EFC11629 - Patient disposition - randomized population .....	79
Table 22 - EFC12347 - Patient disposition - randomized population .....	80
Table 23 - EFC12456 - Primary efficacy analysis - Mean change in HbA1c (%) from baseline to Month 6 using MMRM analysis - mITT population .....	83
Table 24 – EFC12456 - Mean daily insulin doses .....	84
Table 25 – EFC12456 – Selected secondary efficacy endpoints – Number (%) of patients – mITT population .....	87
Table 26 - EFC12456 - Secondary efficacy endpoint- Summary of mean change in FPG (mg/dL) from baseline to endpoint (Month 6) using MMRM analysis- mITT population.....	88
Table 27 - EFC11628 - Main efficacy analysis - Mean change in HbA1c from baseline to endpoint (Month 6) using LOCF procedure – mITT population.....	93
Table 28 - EFC11628 - Incidence of patients (%) with at least one severe and/or confirmed nocturnal hypoglycemia (plasma glucose ≤ 70 mg/dL) between hours of 00:00 and 05:59 during month 3 to month 6.....	96

Table 29 - EFC11628 - Selected secondary efficacy endpoints - Number (%) of patients – mITT population .....	97
Table 30 - EFC11628 - Mean change in FPG (mg/dL) from baseline to Month 6 using LOCF procedure - mITT population.....	98
Table 31 - EFC11629 - Main efficacy analysis - Mean change in HbA1c (%) from baseline to endpoint (Month 6) using LOCF – mITT population.....	104
Table 32 - EFC11629 - Number (%) of patients with at least one nocturnal hypoglycemia event occurring between Week 9 and endpoint (Month 6) (using LOCF procedure).....	107
Table 33 - EFC11629 - Selected secondary efficacy endpoints –Number (%) of patients- mITT population .....	107
Table 34 - EFC11629- Other secondary efficacy endpoints- Mean change in FPG (mg/dL) from baseline to endpoint (month 6) using LOCF procedure - mITT population.....	109
Table 35 - EFC12347- Main efficacy analysis - Mean change in HbA1c (%) from baseline to endpoint (Month 6) using MMRM analysis - mITT population.....	115
Table 36 - EFC12347- First main secondary efficacy endpoint - Number (%) of patients with at least one nocturnal hypoglycemia [00:00 to 05:59] occurring between start of Week 9 and Month 6, indicated as severe and/or confirmed by plasma glucose $\leq$ 3.9 mmol/l (70 mg/dL) – mITT.	118
Table 37 - EFC12347 - Selected secondary efficacy endpoints- Number (%) of patients –mITT population .....	119
Table 38 - EFC12347 - Other secondary efficacy endpoint - Mean change in FPG (mg/dL) from baseline to endpoint (Month 6) using MMRM analysis - mITT population .....	120
Table 39 - Overview of Clinical Safety Data.....	127
Table 40 - Exposure to investigational product during the main on treatment period: T1DM and T2DM study pools - Safety population.....	132
Table 41 - Demographics and baseline characteristics: T1DM and T2DM study pools - safety population. ....	133
Table 42 – Patient deaths for HOE901-U300 and Lantus up to the cutoff date of 29 October 2013 .....	137
Table 43 - Nonfatal SAEs by primary SOC and PT during the main on-treatment period: T1DM and T2DM study pools - Safety population.....	143
Table 44 - Reasons for treatment discontinuation in the T1DM population - Randomized population .....	151
Table 45 - Reasons for treatment discontinuation in the T2DM population - Safety population	152
Table 46 - Summary of “Other reasons” leading to treatment discontinuation for T2DM studies combined (EFC11628, EFC11629, and EFC12347) .....	153
Table 47 - TEAEs leading to permanent treatment discontinuation by primary SOC during the main treatment period: T1DM and T2DM study pools - safety population .....	153
Table 48 - Number (%) of patients with at least one hypoglycemia event during the main on-treatment period for all hypoglycemia categories: T1DM studies - Safety population.....	157
Table 49 - Number of hypoglycemia events per patient-year during the main on-treatment period: T1DM studies-Safety population.....	161
Table 50 Number (%) of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by study period: T1DM EFC12456.....	163

Table 51 - Number (%) of patients with at least one hypoglycemia event during the main 6-month on –treatment period for all hypoglycemia categories: T2DM- EFC11628-Safety population .....	165
Table 52 - Number (%) of patients with at least one hypoglycemia event during treatment start to Week 8 and Week 9 to Month 6 – EFC11628 .....	166
Table 53 - Number (%) of patients with at least one hypoglycemia event during the main 6-month on –treatment period for all hypoglycemia categories: T2DM- EFC11629 - Safety population .....	167
Table 54 - Number (%) of patients with at least one hypoglycemia during treatment start to Week 8 and Week 9 to Month 6 – EFC11629 .....	168
Table 55 - Number (%) of patients with at least one hypoglycemia event during the main 6-month on –treatment period for all hypoglycemia categories: T2DM- EFC12347-Safety population .....	169
Table 56 - Number (%) of patients with at least one hypoglycemia during treatment start to Week 8 and Week 9 to Month 6 – EFC12347 .....	170
Table 57 - Number of hypoglycemic events per patient-year during the main 6-month on-treatment period-T2DM studies-Safety population .....	171
Table 58 - Adverse events of special interest .....	172
Table 59 - Number (%) of patients experiencing at least one TEAE by prespecified MedDRA Queries and Preferred Term- Local tolerability injection site during the main on-treatment period- Safety population.....	174
Table 60 - Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term – Hypersensitivity reactions during the main 6-month period- Safety population.....	174
Table 61 – Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term – Cancer during the main on-treatment period: T1DM and T2DM study pools- Safety population.....	177
Table 62 – Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term –Cardiovascular death, non-fatal MI, non-fatal stroke during the main on-treatment period –Safety population .....	178
Table 63 – Hepatic TEAEs by primary SOC and PT during the main on-treatment period: T1DM and T2DM study pools – Safety population .....	180
Table 64 - All patients in Phase2/3 database who overdosed with IMP (symptomatic and asymptomatic).....	182
Table 65 - TEAEs occurring in $\geq 5\%$ of T1DM patients in HOE901-U300 and Lantus groups, arranged by Preferred term, during the on-treatment 6 month period (T1DM safety population) .....	184
Table 66 – TEAEs occurring in $\geq 5\%$ of a pool of T2DM patients in HOE901-U300 and Lantus groups, arranged by Preferred term, during the on-treatment 6 month period (T2DM safety population) .....	185
Table 67 – Risk difference (95% CI) of common TEAE (s) by primary SOC, HLT and PT during the main on-treatment period: T1DM study pools – Safety population .....	186
Table 68 - Risk difference (95% CI) of common TEAE (s) by primary SOC, HLT and PT during the main on-treatment period: T2DM study pools – safety population .....	189

Table 69 – Summary of post-baseline data collected for laboratory, vital signs, EKG and immunogenicity in the Phase 2/3 program .....	193
Table 70 - Characteristics of EFC11628 and EFC11629 substudies .....	196
Table 71 - Substudy EFC11628 - Patient disposition .....	201
Table 72 - Substudy EFC11628 - Important protocol deviations potentially affecting efficacy analyses- Randomized substudy population .....	201
Table 73 - Substudy EFC11628 - participant baseline characteristics-Randomized substudy population .....	203
Table 74 - Patients by injection interval between 2 consecutive injections- Safety substudy population – EFC11628 .....	205
Table 75 - Substudy EFC11628 - Main efficacy analysis- Mean change in HbA1c (%) from baseline (Month 6) .....	206
Table 76 - Substudy EFC11629 - analysis population.....	208
Table 77 - Substudy EFC11629 - protocol deviations potentially impacting efficacy analyses- Randomized substudy population .....	209
Table 78 - Substudy EFC11629 - Antidiabetic medications taken by patients- Safety substudy population .....	210
Table 79 – Substudy EFC11629 - Demographics and patient characteristics at baseline- Randomized substudy population .....	211
Table 80 - Patients by injection interval between 2 consecutive injections- Safety substudy population – EFC11629 .....	212
Table 81 - Substudy EFC11629 - Main efficacy analysis - Mean change in HbA1c (%) from baseline (Month 6) .....	213
Table 82 - EFC 12456 - Safety population with at least one AIA status during the main 6-month on treatment period who experienced severe hypoglycemia. ....	216
Table 83 - EFC 12456-Safety population with at least one AIA status during the main 6-month on treatment period who experienced severe hypoglycemia by AIA titer.....	217
Table 84 – Number (%) of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by anti-insulin antibody status during the main treatment period: T2DM studies .....	218
Table 85 – Number (%) of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by anti-insulin antibody titer categories during the main treatment period: T2DM studies.....	219
Table 86 – Change in HbA1c from baseline to endpoint (Month 6) in patients with high titers	220
Table 87 – Change in insulin doses from the conclusion of the 12-month on-treatment period to the 1 <sup>st</sup> week of the follow up period across completed trials EFC11628 and EFC11629 .....	221
Table 88 – PDY12777 - Change in insulin doses from the conclusion of the 16-week study to the 1 <sup>st</sup> week of the follow up period .....	222
Table 89 - Post treatment medications: Anti-diabetic insulinic medications - Number of patients by basal/mealtime insulin category and standardized medication name - 4-week follow-up population – EFC11628 .....	223
Table 90 – Post treatment medications: Anti-diabetic insulinic medications - Number of patients by basal/mealtime insulin category and standardized medication name - 4-week follow-up population – EFC11629 .....	225

Table 91 – Number (%) of patients who used post-treatment antidiabetic medications in study  
PDY12777..... 228

## Table of Figures

Figure 1 - TDR11626 - 36-hour mean smoothed glucose infusion rate profiles at steady state for 0.4 U/kg Lantus and 0.4 U/kg HOE901-U300 .....	17
Figure 2 - Mean (SD) predose insulin glargine M1 concentration-time profile .....	28
Figure 4 – Study TDR11626 - Mean (SD) serum insulin glargine concentration-time profiles of 0.4, 0.6 U/kg U300, as well as 0.4 U/kg U100 at steady state.....	30
Figure 5 - EFC12456 - Study Design .....	45
Figure 6 - EFC11628 - Study design .....	50
Figure 7 - EFC11629 - Study design .....	54
Figure 8 - EFC12347 - Study design .....	57
Figure 9 – HbA1c reductions (mITT population) – treatment difference in LS Mean change from baseline .....	60
Figure 10 - EFC 12456 - Primary Efficacy Endpoint - Mean (+/- SE) in HbA1c (%) by visit during the main 6-month on-treatment period - mITT population .....	82
Figure 11 - EFC12456 - Mean (+/- SE) average daily basal and mealtime insulin dose (U) by visit during the main 6-month on-treatment period - mITT population .....	85
Figure 12 – EFC12456 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on treatment period mITT population.....	85
Figure 13 – EFC12456 - 24-hour average plasma glucose based on 8-point profile SMPG (mg/dL; mean ± SE) by visit (main 6-month on-treatment period; mITT population) .....	89
Figure 14 – EFC12456 - Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period .....	90
Figure 15 - Subgroup analyses on primary efficacy endpoint- Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using MMRM analysis by baseline characteristics- mITT population.....	91
Figure 16 - EFC11628 - Main efficacy analysis – Mean HbA1c (%) by visit during the main 6-month on-treatment period - mITT population.....	92
Figure 17 - EFC11628-Average daily basal insulin and mealtime insulin dose (U) by visit during the main 6-month on-treatment period - mITT population.....	94
Figure 18 – EFC11628 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on –treatment period mITT population.....	95
Figure 19 – EFC11628- 24-hour average plasma glucose based on 8-point profile SMPG (mg/dL; mean ± SE) by visit (main 6-month on-treatment period; mITT population) .....	99
Figure 20 - EFC11628 - Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period .....	100
Figure 21 – Subgroup analyses on primary efficacy endpoint – Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using LOCF procedure by baseline characteristics - mITT population.....	102
Figure 22 - EFC11629 -Main efficacy analyses-Mean HbA1c (%) by visit during the main 6-month on-treatment period-mITT population.....	103
Figure 23 - EFC11629- Mean (+/- SE) in average daily insulin glargine dose (Units) over time during the main 6-month on-treatment period - mITT population .....	105
Figure 24 – EFC11629 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on-treatment period in mITT population .....	106

Figure 25- EFC11629 - 24-hour average plasma glucose based on 8-point profile SMPG (mg/dL; mean  $\pm$  SE) by visit (main 6-month on-treatment period; mITT population) ..... 110

Figure 26 – EFC11629- Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period ..... 111

Figure 27 - Subgroup analyses on primary efficacy endpoint - Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using LOCF procedure by baseline characteristics – mITT population ..... 113

Figure 28 - EFC12347 - Mean ( $\pm$ SE) HbA1c (%) by visit during the main 6-month on-treatment period - mITT population..... 114

Figure 29 - EFC12347 - Mean (+/- SE) in average daily insulin dose (U) by visit during the main 6-month on-treatment period - mITT population..... 116

Figure 30 – EFC12347 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on-treatment period in mITT population ..... 117

Figure 31 – EFC12347- Mean (+/- SE) in 24-hour average 8-point SMPG profiles (mg/dL) by visit (main 6-month on-treatment period; mITT population) ..... 121

Figure 32 – EFC12347 – Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period ..... 122

Figure 33 - Subgroup analyses on primary efficacy endpoint - Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using MMRM analysis characteristics - mITT population ..... 124

Figure 34 - Forest plot of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator): T1DM studies- Safety population. .... 159

Figure 35 - Forest plot of number of hypoglycemia events per patient-year (severe hypoglycemia as per investigator) during the main-on treatment period: T1DM studies- Safety population ... 162

Figure 36 – Patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by study period: T2DM studies, safety population..... 164

Figure 37 - Study design Substudy EFC11628 and EFC11629..... 199

Figure 38 - EFC 11628 substudy and EFC11629 patient visits..... 200

Figure 39 - Definitions of compliance based on 2 consecutive injections of both adaptable dosing and fixed dosing- substudy EFC11628..... 204

Figure 40 – Substudy EFC11628 - Main efficacy analysis- Mean HbA1c (%) by visit during the 3-month comparative regimen period- mITT substudy population ..... 207

Figure 41 –Substudy EFC11629 - Main efficacy analysis- Mean HbA1c (%) by visit during the 3- month comparative regimen period - mITT substudy population ..... 214

Figure 42 – EFC11628 - Mean ( $\pm$ SE) in average prebreakfast SMPG (mg/dL) by visit from baseline (day 1) to week-4 follow-up – 4-week follow-up population..... 224

Figure 43 - EFC11629 - Mean ( $\pm$ SE) in average prebreakfast SMPG (mg/dL) by visit from baseline (day 1) to week-4 follow-up - 4-week follow-up population ..... 226

### List of Abbreviations

ADA:	American Diabetes Association
AE:	adverse event
AHA:	antihyperglycemic agents
AIA:	anti-insulin antibody
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
BG:	blood glucose
BMI:	body mass index
bpm:	beat per minute
CGM:	continuous glucose monitoring
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CPK:	creatine phosphokinase
CSR:	clinical study report
CV:	cardiovascular
DBP:	diastolic blood pressure
DKA:	Diabetic ketoacidosis
ECG:	electrocardiogram
eGFR:	estimated glomerular filtration rate
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GCP:	Good Clinical Practice
HbA <sub>1c</sub> :	glycated hemoglobin A <sub>1c</sub>
HDL-C:	high density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HOE901-U300:	300 U/mL formulation of insulin glargine
HR:	heart rate
ICH:	International Conference on Harmonization
IFG:	impaired fasting glucose
IGT:	impaired glucose tolerance
IM:	intramuscular
IMP:	investigational medicinal product
IND:	Investigational New Drug
ISS:	Integrated Summary of Safety
IV:	intravenous
IVRS:	interactive voice response system
IWRS:	interactive web response system
KM:	Kaplan Meier
LDL-C:	low density lipoprotein cholesterol

M1:	metabolite 21A-Gly-insulin
M2:	metabolite 21A-Gly-des-30B-Thr-insulin
MACE:	major adverse cardiovascular event
MDRD:	modified diet and renal disease
MedDRA:	medical dictionary for regulatory activities
MI:	myocardial infarction
MRI:	magnetic resonance imaging
NDA:	New Drug Application
NIMP:	non-investigational medicinal product
NPH:	neutral protamine Hagedorn
OAD:	oral antihyperglycemic drugs
OR:	odds ratio
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PeRC:	Pediatric Review Committee
PK:	pharmacokinetic
PPSR:	Proposed Pediatric Study Request
PRAC:	Pharmacovigilance Risk Assessment Committee
PREA:	Pediatric Research Equity Act
PT:	preferred term
RBC:	red blood cells
RCT:	randomized clinical trial
RR:	relative risk
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	subcutaneous
SD:	standard deviation
SE:	standard error
SHRB:	Severe Hypoglycemia Review Board
SI:	standard international
SMPG:	self-monitored plasma glucose
SMQ:	standardized MedDRA query
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
USA:	United States of America
WBC:	white blood cells

## 1 Recommendations/Risk Benefit Assessment

Sanofi-Aventis U.S. LLC submitted this 505 (b)(1) NDA for insulin glargine [rDNA origin] injection, 300 Units/mL (HOE901-U300). HOE901-U300 is supplied as a solution for injection in 1.5 mL cartridges that are integrated into a disposable pen-injector (SoloStar®).

The proposed indication for HOE901-U300 (proposed trade name: Toujeo®) is to improve glycemic control in adults with diabetes mellitus.

### 1.1 Recommendation on Regulatory Action

Based on my review of clinical efficacy and safety, I recommend **approval** of this NDA pending agreement with the Sponsor on labeling.

### 1.2 Risk Benefit Assessment

HOE901-U300, if approved, would serve as another therapeutic option for patients with diabetes mellitus in need of basal insulin therapy.

In this section, the risk versus benefit assessment is combined for patients with type 1 (T1DM) and type 2 diabetes (T2DM), since similar efficacy and safety findings were seen in both groups. Overall, the benefit of HOE901-U300 use outweighs its risks.

The benefits associated HOE901-U300 stem from the efficacy results of its clinical program. Across all four, well-powered, pivotal trials (one in T1DM and three in T2DM), the primary efficacy endpoint of non-inferiority of change in HbA1c from baseline to 6 months, defined as the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus <0.4%, was demonstrated.

Furthermore, the generalizability of the efficacy results and patient exposure was adequate in all trials. The efficacy results across the pivotal trials can be reasonably applied to the United States population. All studies met the ICH standards for adequate patient exposure for duration of 6 months.

The Sponsor proposed

(b) (4)





The evaluation of risk focused on reported adverse events, routine laboratory assessments, and immunogenicity assessments. No safety concerns were found by this reviewer. The overall incidence of reported adverse events including deaths, nonfatal serious adverse events, and events leading to dropout was similar between HOE901-U300 and Lantus. Across system organ classes, incidence of reported adverse events was similar between HOE901-U300 compared to Lantus, with the exception of increased cerebrovascular events in the T2DM Lantus group. Most of the patients that made up this imbalance had pre-existing risk factors, other than diabetes. Therefore, I do not believe that this imbalance represents a true risk of Lantus (or a benefit of HOE901-U300).

Although HOE901-U300 is essentially a three times concentrated formulation of Lantus, on a unit to unit basis, HOE901-U300 is not bioequivalent to Lantus. Clinical pharmacology studies suggest that at steady state, 0.4 U/kg of HOE901-U300 has ~73% of the pharmacodynamic (PD) effect, based on AUC<sub>0-24</sub>, as 0.4 U/kg of Lantus. In Phase 3 clinical studies, this difference in PD effect translated into a 7.7% to 14.8% increase in total (U/kg) daily insulin use for HOE901-U300 randomized groups compared to Lantus randomized groups (or 8-9 more total units per day of insulin in the HOE901-U300 groups). Yet similar HbA<sub>1c</sub> at the end of the 6 month trial periods were achieved between HOE901-U300 and Lantus because insulins are titratable. Importantly, the apparent pharmacodynamic differences did not result in differences in adverse events reported during the phase 3 trials between the two insulins (e.g., hyperglycemia) that might be expected if HOE901-U300 were not as effective as Lantus.

A mild, transient increase in fasting hyperglycemia and increased 24-hour average plasma glucose, not favoring HOE901-U300, was observed during the first two weeks of study treatment in the phase 3 studies. However, there is no evidence to suggest that this finding represents a clinically significant difference between the products in the overall management of T1DM or T2DM. In particular, this transient, mild hyperglycemia did not result in any cases of diabetic ketoacidosis or nonketotic hyperosmolarity, other serious adverse events, or adverse events leading to dropouts. Further, the transient, mild hyperglycemia would not be expected to result in any compromise to the long-term prevention of diabetic complications.

HOE901-U300 also appears to have a first dose lag in the onset of action compared with Lantus and takes longer to reach steady state compared with Lantus. The first dose lag time before pharmacodynamic effect of HOE901-U300 may present a theoretical risk of DKA when patients with T1DM are treated via an insulin drip and then converted to HOE901-U300. This scenario was not studied in the HOE901-U300 development program. To help mitigate this potential risk,

I recommend emphasizing the lag time before action in the Warnings and Precautions section of the HOE901-U300 label.

Because insulins are titratable, differences in pharmacodynamic effect of different basal insulins may not be noticeable in clinical practice when converting from insulin with a lower AUC0-24 to an insulin product with a higher AUC0-24. However, in the reverse case, there is a theoretical risk of hypoglycemia. The data in this application show no evidence of an increased risk of hypoglycemia. Although basal insulin dose conversion at the end of the trials was not prespecified in the protocols, of the patients randomized to HOE901-U300, at the end of the trials basal insulin doses were decreased by investigators ranging from 10% to 15% upon converting back to commercial insulin. Perhaps differences in hypoglycemia when converting from an insulin with a lesser pharmacodynamic effect to one with a higher pharmacodynamic effect, (i.e. going from HOE901-U300 to Lantus), were not seen because of decreases in doses upon converting insulins. Labeling information in the Dosing and Administration section should address the issue of converting from HOE901-U300 to Lantus.

### **1.3 Recommendations for Postmarket Risk Management Activities**

None.

There is no current Risk Evaluation and Mitigation Strategy (REMS) for the listed drug Lantus and no safety concern that warrants a REMS for HOE901-U300.

### **1.4 Recommendations for Postmarket Studies/Clinical Trials**

This application triggers the Pediatric Research Equity Act, and therefore, pediatric studies under PREA are recommended. PREA studies have already been reviewed by the Agency and agreed upon with the Sponsor.

Parenteral insulins are currently exempt from the requirement to conduct cardiovascular safety risk assessment studies. There is no safety concern based on the data in this application that suggests a cardiovascular risk.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

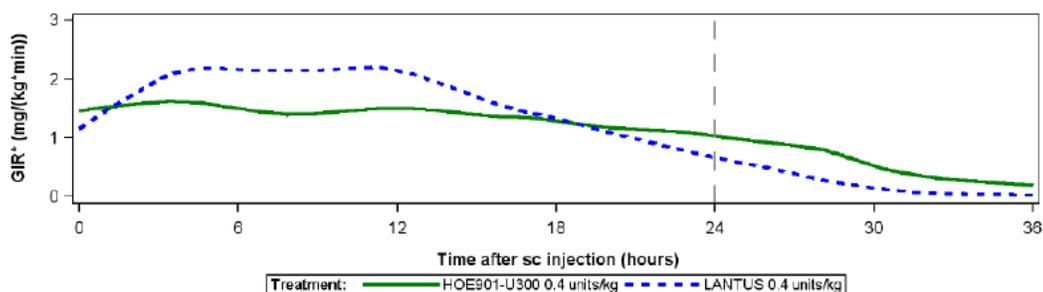
HOE901-U300, insulin glargine [rDNA origin] injection, 300 Units/mL, is a three times concentrated formulation of Lantus (insulin glargine). HOE901-U300 has the same composition as the current commercial formulation of Lantus, with adjustment of three times the amount of active pharmaceutical ingredient and corresponding zinc content.

Insulin glargine is 31B-32B-Di-Arg human insulin, a recombinant (*Escherichia coli* [E coli]) analog of human insulin, with further substitution of asparagine in position A21 by glycine. The predominant circulating metabolite in both Lantus and HOE901-U300 is 21AGly-human insulin (M1 metabolite).

The composition of the drug product includes zinc (b) (4) glycerol (85 percent) (b) (4) hydrochloric acid. (b) (4) sodium hydroxide (b) (4) water (b) (4)

The main difference between HOE901-U300 and Lantus is in the pharmacokinetic (PK)/pharmacodynamic (PD) profiles of the two formulations (Figure 1). Single and multi-dose studies using euglycemic clamps, suggest that insulin HOE901-U300 has a flatter and prolonged time-action profile compared to Lantus at matching doses. This is discussed in more detail in section 4 and in the Office of Clinical Pharmacology review.

**Figure 1 - TDR11626 - 36-hour mean smoothed glucose infusion rate profiles at steady state for 0.4 U/kg Lantus and 0.4 U/kg HOE901-U300**



\* Glucose infusion rate

Local regression smoothing (LOESS), smoothing factor 0.20.

Source: Clinical Overview, Figure 1

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved treatments of T1DM and T2DM include:

- Insulin and insulin analogs
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Inhibitors of alpha-glucosidase
- Analogues of Glucagon-like Peptide 1 (GLP-1)
- Synthetic analogues of human amylin
- Inhibitors of the enzyme dipeptidyl peptidase 4 (DPP4)
- Bile acid sequestrants
- Dopamine agonists
- SGLT-2 inhibitors

### **2.3 Availability of Proposed Active Ingredient in the United States**

Lantus and HOE901-U300 have the same active ingredient, glargine. Lantus was approved for the glycemic control of pediatric and adult patients with T1DM and T2DM on 20 Apr 2000.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Two important safety issues arise with all insulins: hypoglycemia and formation of insulin antibodies.

Hypoglycemia is the most common adverse event of all insulins. The severity of hypoglycemia can result in a range of impairments from temporary to permanent. The risk of hypoglycemia increases with increased intensive glycemic control. Refer to 7.3.4 Significant Adverse Events for further discussion of hypoglycemia.

Exposure to insulin products may elicit the formation of insulin antibodies. The formation of these antibodies may affect efficacy of insulin and require dose adjustment for glycemic control. Refer to section 7.4.6 Immunogenicity for further discussion regarding insulin antibodies.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The following summary of regulatory activity focuses on the clinical communication between the Sponsor and the FDA.

*On April 21, 2006, the Sponsor requested a Type C meeting under IND 049078 (HOE901) to discuss the development plan for a 300 U/mL formulation in a disposable pen device and registration as prior approval supplement. Clarification of development study and bioequivalent study design was answered on July 21, 2006. A Pre-IND FDA response was provided on September 7, 2011, which addressed the following topics:*

(b) (4)



*A series of communications between the FDA and the Sponsor occurred between September 2011 and February 2012: (FDA requested information on September 27, 2011; Sponsor answered on November 7, 2011; FDA responded on February 27, 2012; Sponsor responded on June 4, 2012). During these communications, the major topics discussed included:*

- Clarification of rationale for the Sponsor excluding patients pre-treated with basal insulin other than insulin glargine or NPH
  - Based on clamp studies in type 1 diabetes, change from Lantus to HOE901-U300 was done on a 1:1 (unit: unit) basis. Recommendations for changeover from NPH and detemir to HOE901-U300 were done using Lantus USPI. Exclusion of patients using premix insulins was clarified- because it would lead to patients changing more than one treatment regimen at the start of study with need of additional training and learning period (and concerns of unstable glycemic control).
- FDA recommended that Sponsor should enroll patients with sufficiently high baseline HbA1c (e.g., mean baseline HbA1c ~8.5%) and limit insulin titration to the first 12 weeks of the trial. There should be minimal titration of insulin doses during Months 3-6 with adjustments for safety reasons only.
- FDA asked that the Sponsor consider an assessment of insulin antibodies off treatment.
  - Sponsor stated that it was not feasible to assess reversibility of anti-insulin antibodies in patients enrolled in the Phase 3 trials, since patients require daily insulin therapy and insulin cannot be stopped to test for antibodies.
- FDA recommended the Sponsor use the following MedDRA searches to analyze hypersensitivity reactions in your clinical studies: Angioedema SMQ [Narrow]; Severe cutaneous adverse reactions SMQ [Broad]; and Anaphylactic Responses [High Level Term]. For injection site reactions we recommend the following searches: under System Organ Class “General Disorders and Administration Site Conditions”: High Level Group Term “Administration site reactions” and High Level Terms “Administration site reactions NEC”, “Infusion site reactions” and “application and instillation site reactions”.
- FDA recommended that the Sponsor capture information on site of administration (abdomen, thighs, and upper arms) to explore whether different sites of administration influence efficacy or safety.
  - For EFC11628 and EFC11629, the Sponsor reported injection site verbatim on the (CRF) only in case of a reported injection site reaction. For the remaining trials, EFC12456 and EFC12347, the Sponsor followed the FDA advice.
- FDA recommended algorithm for prandial insulin titration.
  - Sponsor stated that titration of prandial insulin would be based on investigator preference.
- The FDA requested clarification of the **nocturnal hypoglycemia** endpoint.

- 1) Why is nocturnal hypoglycemia defined as occurring between 11 PM and 7 AM, since the patient may not be sleeping then? If patients are awake, during this period, they are more readily to detect hypoglycemia than patients who are asleep.
  - The Sponsor adjusted the nocturnal time period from 23.00 to 7.00 to 24.00 -05.59 hours in all Phase 3 studies. Nocturnal hypoglycemia was defined by this time period regardless of if patient was awake or asleep. The reason for the time adjustment was to try to exclude confounding factors (i.e. exercise, food etc., mealtime insulin...). For studies EFC12456 and EFC12347, the Sponsor recorded the patient's sleep status (asleep, awake and woke up) when a hypoglycemia episode was experienced during the nighttime hours.

The FDA then clarified that the proposal to assess the risk of hypoglycemia during this time period is acceptable if the Sponsor's intends to assess the risk of hypoglycemia during the 11 pm to 7 am time period, regardless of whether patients are asleep. However, if the Sponsor intends to assess the risk of hypoglycemia during sleep, the Agency recommends that the Sponsor revise its proposal.

- 2) The FDA suggested that the Sponsor base the nocturnal hypoglycemia endpoint on the entire treatment period; or perform additional analyses examining months 0-3 and 3-6 separately.
  - Per the Sponsor, the nocturnal hypoglycemia endpoint is based on data during Months 3-6. As part of the pre-specified hypoglycemia analyses for Phase 3, rates of various types of hypoglycemia (including nocturnal hypoglycemia) will be presented by study period to evaluate the potentially increased risk of hypoglycemia during the initial phase after the change to a new insulin regimen and during the maintenance period.
- 3) Inclusion of "probable symptomatic hypoglycemia" in the nocturnal hypoglycemia definition may lead to inclusion of events that do not truly represent hypoglycemia.
  - In the current phase 3 protocols, nocturnal hypoglycemia events to be included in the analysis of the first main secondary endpoint include: Severe hypoglycemia, documented symptomatic hypoglycemia; confirmed by plasma glucose  $\leq 70$  mg/dL, asymptomatic hypoglycemia; confirmed by plasma glucose  $\leq 70$  mg/dL, and probable symptomatic hypoglycemia
  - The Sponsor amended protocols to consider only the categories of severe hypoglycemia and hypoglycemia confirmed by plasma glucose data in the analysis of the first main secondary endpoint and excluded from the analysis of the main secondary endpoint, "relative hypoglycemia," and "probable symptomatic hypoglycemia."
- FDA expressed concern over the submitted Phase 3 trials that administered glargine U-100 and U-300 in the evening hours only, since glargine U-100 label states glargine can be administered at any time of the day.
  - The Sponsor informed the Agency that the efficacy and distribution of hypoglycemia of HOE901- U300 when injected at other time points than in the evening would be evaluated in Phase 3 study EFC12456.

On August 26, 2011 the initial IND submission for HOE901-U300 was placed under IND 112400)

*On October 26, 2011, the FDA sent an Advice/Information request, which was answered by the Sponsor on November 21, 2011. In this communication, the Agency addressed two statistic concerns:*

- Due to the National Academy of Science Report on “The Prevention and Treatment of Missing Data in Clinical Trials,” the Agency asked to see other analyses that accounted for dropout patterns. The Agency also recommended that for all endpoints, protocols should examine potential mechanisms, which may cause data to be missing, and how the analyses and imputation methods may affect Type I error.
  - The Sponsor stated that for studies EFC11628 and EFC11629, missing efficacy endpoint values would be imputed from the last available post-baseline on-treatment value before the visit using the LOCF method.
- The Agency asked that the first main secondary efficacy endpoint, (nocturnal hypoglycemia), should be based on the mITT population and not the safety population.

*On August 9, 2011, the Sponsor submitted questions to the Agency that were answered on September 2, 2011. On October 20, 2011, the Sponsor replied to the Agency’s comment and the FDA responded again in May 3, 2012. In these communications, the following topics were discussed:*

- The Agency was concerned (b) (4)  

- The Sponsor planned (b) (4)  

- The Agency agreed that 6 months of treatment data at the time of the NDA submission is acceptable.
- The Sponsor stated that the main secondary endpoints (i.e., nocturnal hypoglycemia, preinjection plasma glucose) would be tested in a hierarchical order. The Agency agreed that type 1 error should be controlled (b) (4)  


 (b) (4)

[REDACTED] (b) (4)

The FDA expressed concerns

[REDACTED] (b) (4)

The Agency expressed concern (b) (4)

- The Sponsor analyzed the pre-injection plasma glucose [REDACTED] (b) (4)
- The FDA clarified that [REDACTED] (b) (4) will be a review issue that would take into account the study results as well as the concerns raised above.

*Communications between the FDA on August 12, 2013 and response by Sponsor on September 12, 2013 addressed statistical comments.*

- The FDA noted that the Sponsor used the Last Observation Carried Forward (LOCF) method for dealing with missing data, which is no longer recommended by the Division. The Agency suggested that the Sponsor submit an amendment to the SAP to propose a statistical analysis which does not rely on LOC and which is in line with NAS recommendations before submitting the NDA for each pivotal phase 3 studies. In response, the Sponsor proposed to use the Mixed Model with Repeated Measures (MMRM) instead of LOCF for studies EFC12347 and 12456 and not for EFC11628 and EFC11629 (since the latter had their efficacy and safety analyses done).

*In November 20, 2013, the official Pre-NDA meeting meetings were released on November 20, 2013, which included the submitted Pre-NDA meeting briefing package questions and FDA answers.*

- The Agency agreed with the Sponsor's proposal for the immunogenicity assessment. The Sponsor would present this assessment for trials EFC11628 and EFC11629 in the NDA and the AIA results would be presented after completion of the 12-month study duration for patients in EFC12347 and EFC12456.

- At the time of the meeting, the Agency did not agree [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] The FDA agreed to consider these additional parameters to support the Sponsor's claim during the review process.
- The Agency was concerned [REDACTED] (b) (4)  
[REDACTED]
- The Agency confirmed agreement with the Sponsor's Pre-IND briefing package. In this document, the Sponsor stated that Adjudication of cardiovascular events is not deemed necessary taking into consideration the large safety experience with insulin glargine, which does not indicate an identified risk regarding an increase of cardiovascular events. However, the Agency stated that if a cardiovascular safety signal emerged during review, that additional information/analysis might be needed.
- The Agency again stated its disagreement with the Sponsor that a statement [REDACTED] (b) (4) could not be included in the product information of HOE901-U300 since this was a review issue. As previously stated, in the pre-IND advice letter, the Agency had concerns [REDACTED] (b) (4)  
[REDACTED] the following concerns were expressed by the FDA:
  - Evaluation of hypoglycemic risk should be based on the entire treatment intervention phase (from titration to maintenance phase), not as proposed by the Sponsor, from week 9 to month 6 of the trials.
  - The Agency disagreed [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] The Agency prefers that trials demonstrate a benefit for an endpoint based on severe hypoglycemic events because this definition is the most specific.
  - Other Agency's concerns included the proposal [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]



The Sponsor documented protocol violations when they occurred. Site closures occurred in two locations in the United States affecting study EFC11628 (7 randomized patients) and EFC11629 (no randomized patients). Sites were closed due to ongoing noncompliance with the clinical protocol and violations of Good Clinical Practice. The Sponsor notified the FDA of these site closures in writing.

The Office of Scientific Investigations (OSI) inspected six sites (five domestic and one foreign). These sites were involved in the following studies: EFC12347, EFC12456, and EFC11628. These sites were selected due to the enrollment of large numbers of study subjects and due to high number of treatment responders. For five site inspections, the inspectional findings were consistent with NAI (No Action Indicated); one site is pending review of Establishment Inspection Reports (EIR). In general, the inspections of six clinical sites support the validity of data as reported by the Sponsor under this NDA. Refer to Dr. Kleppinger's OSI review for further details.

#### Amendments:

Protocol amendments were made for: EFC11628 (five amendments), EFC11629 (five amendments), EFC12347 (one amendment), EFC12456 (one amendment), PDY12777 (three amendments). None of these affected the studies' validity.

#### Audits:

Independent audits were conducted by Research and Development Clinical & Medical Quality Operations based on the Sanofi Quality Documents in sites around the world for studies: EFC11628 (17 audits), EFC11629 (17 audits), EFC12347 (18 audits), EFC12456 (13 audits).

### **3.3 Financial Disclosures**

The Sponsor has adequately disclosed financial arrangements with the clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical investigators*. These arrangements do not raise any questions about the integrity of the data submitted in the NDA. See Appendix: 9.4 *Clinical Investigator Financial Disclosure Review Template* for further details.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

For a detailed review of CMC, refer to the review by Xavier Ysern. Dr. Ysern recommends approval of this NDA.

The divisions of CDRH-Devices (Ryan McGowan), DMEPA (Sarah Vee) and Human Factors (Quynh Nguyen) also reviewed the pen injector device constituent as part of this application. There were no CDRH device or human factors related deficiencies for this application.

As Toujeo, insulin glargine is available as solution for injection containing 10.91 mg/mL insulin glargine [equivalent to 300 U (units) of insulin glargine]. During development only minor changes were made in the manufacturing procedure to adapt the process to the scaled up batch sizes. In addition, the presentation was changed (b) (4) to a 1.5 mL cartridge. As demonstrated by stability studies, Dr. Ysem concluded that these changes had no impact on the overall quality of the drug product.

#### **4.2 Clinical Microbiology**

For detailed review of microbiology, refer to the review by Neal Sweeney. Dr. Sweeney recommends approval of this NDA.

HOE901-U300 is a sterile solution for parenteral use. (b) (4)

#### **4.3 Preclinical Pharmacology/Toxicology**

For a detailed review of the Preclinical Pharmacology/Toxicology, refer to the review by Jeff Quinn. Dr. Quinn recommends approval of this NDA.

As agreed at the Pre-NDA meeting, since the active substance (insulin glargine) is the same in both Lantus and HOE901-U300, the Sponsor cross-referenced the nonclinical studies of Lantus in support of this application.

The toxicity studies of Lantus have been extensively assessed by the Sponsor in carcinogenicity, local tolerability, reproductive, and mutagenicity studies.

Although the Sponsor did not develop a dedicated non-clinical program for HOE901-U300, before the initiation of clinical trials, the Sponsor tested the tolerability of HOE901-U300 compared to Lantus in rabbits. In Study TOL1099, tolerability was assessed via indicated and non-indicated routes of administration, including subcutaneous injection (indicated for human use), intramuscular, intravenous, and paravenous injections (representing potential false routes of administrations). The results of this study showed good local tolerability of both HOE901-U300 and Lantus. This study supported the use of the 300 U/mL formulations in human subjects.

#### **4.4 Clinical Pharmacology**

A detailed review of clinical pharmacology is being conducted by Dr. Johnny Lau. At the time of this review Dr. Lau's review has not been finalized.

#### 4.4.1 Mechanism of Action

HOE901-U300 like endogenous and insulin analogues, acts via the insulin receptor to regulate glucose metabolism. HOE901-U300 lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and inhibits hepatic glucose production.

#### 4.4.2 Pharmacodynamics

The information in this section is obtained from Dr. Lau's preliminary review. Changes in nomenclature were made by Dr. Lau for consistency (for example, in his review U300 refers to HOE901-U300, while U100 refers to Lantus).

Pharmacodynamic studies showed that HOE901-U300 does not have equivalent bioavailability to Lantus. Equal metabolism of insulin glargine (regardless of the formulation, HOE901-U300 or Lantus) was confirmed. The main metabolite in both HOE901-U300 and Lantus was M1 (21<sub>A</sub>-Gly-human insulin).

There are four clinical pharmacology qualities of HOE901-U300 that differ from Lantus and that may inform the safety, efficacy and labeling of this drug product. These include (1) PD difference, (2) time to reach steady state, (3) lag time of onset of action for single dose, and (4) duration of action.

These elements are addressed in detail below.

##### Pharmacodynamic difference

The Sponsor's PD multiple dose study results are shown in Table 1. Per this evaluation of the  $GIR-AUC_{0-24h}$  treatment ratio of 0.4 U/kg of HOE901-U300 divided by 0.4 U/kg of Lantus, shows that HOE901-U300 has ~ 73% of the PD effect as Lantus (for this dose at steady state).

**Table 1 – Comparison of PD effect at steady state of U300 vs. U100 glargine**

Treatment Ratio	Parameter	Estimate	90% CI	95% CI
0.4 U/kg U300 ÷ 0.4 U/kg U100	$GIR_{max}$	0.81	0.68 – 0.97	0.65 – 1.01
	$GIR-AUC_{0-24h}$	0.73	0.56 – 0.94	0.53 – 0.99
	$GIR-AUC_{0-36h}$	0.85	0.70 – 1.03	0.67 – 1.08
0.6 U/kg U300 ÷ 0.4 U/kg U100	$GIR_{max}$	1.20	0.88 – 1.62	0.83 – 1.73
	$GIR-AUC_{0-24h}$	1.46	0.96 – 2.21	0.88 – 2.43
	$GIR-AUC_{0-36h}$	1.65	1.11 – 2.46	1.02 – 2.70

U100 = LANTUS; U300 = HOE901-U300; Study TDR11626; steady state; 8<sup>th</sup> day of 8 daily doses. Source, Tables 12, 13 study CSR

**Reviewer's comments: The lower PD effect of HOE901-U300 compared to Lantus is more salient in the clinical pharmacology studies than in the clinical studies (see section 6 *Review of Efficacy*). Table 1 suggests that a dose of 0.4 U/kg of HOE901-U300 is about 73% of a dose of 0.4 U/kg of Lantus. I note that the  $GIR-AUC_{0-36h}$  shows a more similar PD effect**

**between Lantus and HOE901-U300 consistent with the observation that HOE901-U300 action extends beyond 24 hours.**

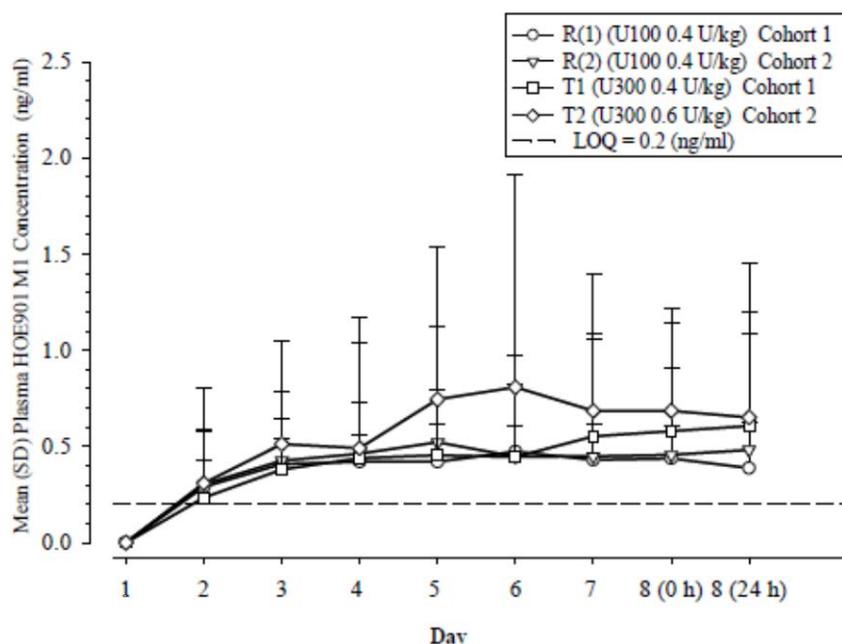
**Concern of what lower PD effect of HOE901-U300 may mean in regards to labeling and safety is addressed in section 1.2 Risk Benefit Assessment.**

Time to reach steady state (per Dr. Lau’s review)

Study TDR11626 provides information regarding the time to reach steady state for one dose of Lantus and two different doses of HOE901-U300 glargine. The daily pre-dose plasma insulin glargine concentrations were quantifiable in only 1 of 12 patients in both the 0.4 U/kg HOE901-U300 dose group and the 0.6 U/kg HOE901-U300 dose group. Thus, it is difficult to determine the time for HOE901-U300 to reach steady state through assessment of pre-dose plasma insulin glargine concentrations. However, visual inspection showed that insulin glargine’s M1 metabolite (major circulating metabolite) reached steady state on Day 7 in the 0.4 U/kg HOE901-U300 daily dose group and on Day 5 in the 0.6 U/kg HOE901-U300 daily dose group (Figure 2). However, insulin glargine and M2 PK parameters are quantifiable only in some patients.

Although the Sponsor reported inconsistent times (in different parts of the NDA submission), for HOE901-U300 to reach steady (from 3.4 to 7 days), the clinical pharmacology reviewer suggests that HOE901-U300 reaches steady state at 5-7 days after 0.4 U/kg to 0.6 U/kg SC administration in T1DM patients.

**Figure 2 - Mean (SD) predose insulin glargine M1 concentration-time profile**



Source: Study CSR, Figure 23

**Reviewer’s comment: The time for HOE901-U300 to reach steady state ranged from 5 days (in 0.6 U/kg dose group) to 7 days (in 0.4 U/kg dose group). The longer time to reach**

**steady state may have implications on the frequency of titration that clinicians will have to recommend to patients. Theoretically, titrating aggressively and more frequently than every 5 days could lead to risk of hypoglycemia. In the clinical trials of this development program, however, despite the basal titration schedule of no more frequently than every 3-4 days, there was no increased patient incidence of severe hypoglycemia. Therefore, I believe that the titration of every 3-4 days is appropriate and supported by the phase 3 trials.**

Lag time in onset of action for single dose (per Dr. Lau's review)

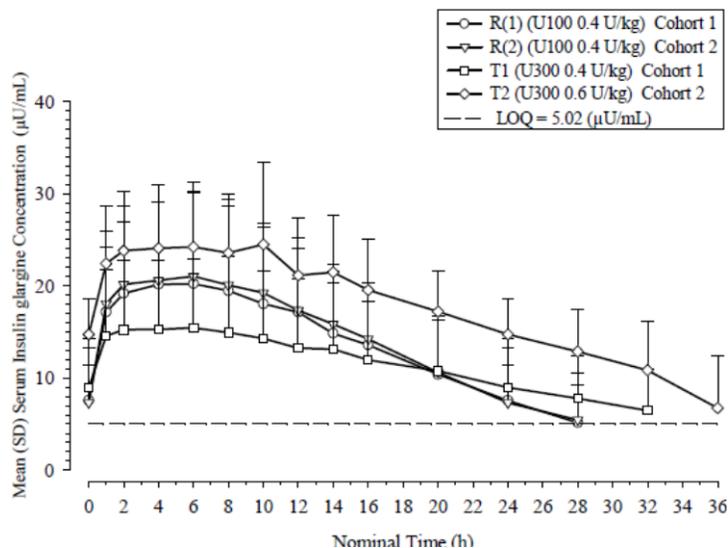
Refer to Dr. Lau's review for information regarding the first dose lag time. At the time of my review submission, the Office of Clinical Pharmacology (OCP) review is not completed. However on multiple discussions with OCP, they confirmed a longer lag time (~10 hours) for insulin action applicable to the first dose of HOE901-U300.

**Reviewer's comment: The lag time does not have long lasting implications, since patients will reach steady state (after 5-7 days) of HOE901-U300 use, and the lag time will no longer be applicable. The most concerning scenario where the lag time may have a safety concern is for the T1DM patient who is transitioning from insulin drip to subcutaneous insulin. These patients may be at increased risk of DKA if the basal dose of HOE901-U300 takes 10 hours to begin glycemic control after a first dose. I believe that this potential risk can be mitigated through labeling.**

Duration of action (from Dr. Lau's review)

The steady state profiles of serum insulin glargine for treatments with HOE901-U300, 0.4 U/kg (T1) and 0.6 U/kg (T2) were generally flat and displayed detectable exposure at the corresponding mean concentrations until 32 and 36 hours post-dose, respectively (Figure 3). The mean insulin glargine concentrations for the reference treatments with 0.4 U/kg Lantus R1 and R2 were nearly overlapping. Serum insulin glargine concentrations were quantifiable until 28 hours after SC administration of Lantus.

**Figure 3 – Study TDR11626 - Mean (SD) serum insulin glargine concentration-time profiles of 0.4, 0.6 U/kg U300, as well as 0.4 U/kg U100 at steady state.**



Source: Study report, Figure 10

#### 4.4.3 Pharmacokinetics

See above for combined discussion regarding Pharmacokinetic/dynamic review issues.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The clinical development program of this NDA206538 includes 13 studies

- 6 Phase 1 clinical pharmacology trials
- 1 Phase 2 therapeutic confirmatory trial
- 6 Phase 3 therapeutic confirmatory trials

As of 29 October 2013 (cut-off date for the dossier), 6 Phase 1 studies and 1 Phase 2 study were completed. At the time of the dossier cut-off, 4 global Phase 3 studies (EFC11628, EFC11629, EFC12347, and EFC12456) had completed the main 6-month on-treatment periods, which serves as the basis for efficacy and safety evaluation of HOE901-U300 in the NDA.

Between the dossier cut-off date (29 October 2013) and the 120-day safety update cut-off date (21 April 2014), 2 of the 4 global Phase 3 studies (EFC11628 and EFC11629) completed the 6-month safety extension period (plus 4-week post-treatment follow-up period), and both Japanese Phase 3 studies (EFC12449 and EFC12512) completed the main 6-month on-treatment period.

Table 2 shows the Phase 3 pivotal studies and the 2 substudies that were reviewed in support of the efficacy and safety of this NDA. The safety results of Phase 2 Study PDY12777 (Table 3) were included in my assessment for safety only (not on efficacy). Table 4 shows human studies

Clinical Review

Tania A. Condarco, M.D.

NDA206538

Toujeo, insulin glargine [rDNA origin] injection, 300 Units/mL

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performed by the Sponsor for evaluation of bioavailability, bioequivalence, pharmacodynamics, efficacy, and safety.

**Table 2 - Table of four pivotal trials and two substudies supporting the clinical efficacy and safety evaluation for this NDA**

	Studies in 1DM	Studies in T2DM		
	EFC12456	EFC11628	EFC11629	EFC12347
Population	T1DM on <b>basal</b> insulin in combination with <b>mealttime</b> insulin analog	T2DM on <b>basal</b> insulin in combination with <b>mealttime</b> insulin analog	T2DM on <b>basal</b> insulin in combination with <b>OAD</b>	<b>Insulin-naïve</b> T2DM not adequately controlled on <b>non-insulin AHA</b>
Region	North America, Europe, Japan	North America, South America,	North America, South	North America, Europe, Japan
Comparator	Lantus	Lantus	Lantus	Lantus
Randomization	1:1:1:1 <ul style="list-style-type: none"> <li>• HOE901-U300 morning injection</li> <li>• HOE901-U300 evening injection</li> <li>• Lantus morning injection</li> <li>• Lantus evening injection</li> </ul>	1:1	1:1	1:1
Main Objectives	Efficacy and safety	Efficacy and safety	Efficacy and safety	Efficacy and safety
Duration of treatment	6 months (main study period) 6 months comparative extension period <sup>a</sup>	6 months (main study period) 6 months comparative extension period <sup>a</sup>	6 months (main study period) 6 months comparative extension period <sup>a</sup>	6 months (main study period) 6 months comparative extension period <sup>a</sup>
Number of patients randomized	HOE901-U300: 274 Lantus: 275	HOE901-U300: 404 Lantus: 403	HOE901-U300: 404 Lantus: 407	HOE901-U300: 439 Lantus: 439
<b>3-month substudies</b>	NA			NA
Patient population:		Patients randomized and treated with HOE901-U300 during the main study period	Patients randomized and treated with HOE901-U300 during the main study period	
Comparison		HOE901-U300 injection intervals <ul style="list-style-type: none"> <li>• at fixed 24-hour intervals</li> <li>• at intervals of 24±3 hours</li> </ul>	HOE901-U300 injection intervals <ul style="list-style-type: none"> <li>• at fixed 24-hour intervals</li> <li>• at intervals of 24±3 hours</li> </ul>	
Randomization		1:1	1:1	
Objective:		Efficacy and safety	Efficacy and safety	
Duration:		3 months (Month 6 – Month 9 extension period)	3 months (Month 6 – Month 9 extension period)	
Number of patients randomized		Fixed intervals: 53 Adaptable intervals: 56	Fixed intervals: 44 Adaptable intervals: 45	

Source: Sponsor's Clinical Overview, Table 5 <sup>a</sup> Extension period ongoing at the time of the dossier cut-off date; results of safety extension periods not included in the dossier. OAD = oral antihyperglycemic drugs; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; CGM = continuous glucose monitoring; NA = not applicable.

**Table 3 - Phase 2 study, PDY12777 (supporting safety assessment only)**

Studies in T1DM	PDY12777 Phase 2; Exploratory CGM study
Population	T1DM on basal insulin in combination with mealtime insulin analog
Region	USA
Comparator	Lantus
Randomization	1:1:1:1 HOE901-U300 injection sequence: <ul style="list-style-type: none"> <li>• Period A morning --&gt;Period B evening</li> <li>• Period A evening --&gt; Period B morning</li> </ul> Lantus injection sequence <ul style="list-style-type: none"> <li>• Period A morning --&gt;Period B evening</li> <li>• Period A evening --&gt;Period B morning</li> </ul>
Main Objectives	Efficacy and safety
Route Injection device:	Once daily SC injection HOE901-U300 and Lantus: Half-unit U100-syringe; whole-unit U100-syringe for Lantus doses >30 units
Duration of treatment	16 weeks (2 x 8 weeks)
Number of patients randomized	HOE901-U300: 30 Lantus: 29

Source: Modified Table 5 in Clinical Overview

**Table 4 – Other clinical studies performed by the Sponsor (not supporting the efficacy and safety review for this NDA, including Clinical Pharmacology studies)**

Biopharmaceutical studies-comparative bioavailability and bioequivalence studies			
Study	Population Location of study(ies) N randomized	Study objective(s)	Study design
PKD10086	Healthy subjects Germany (1 center) N=24	- To assess the average bioequivalence of Lantus and HOE901-U300 in bioavailability and bioefficacy using the euglycemic clamp technique -To assess the safety and tolerability of HOE901-U300	Randomized, controlled, single-blind, 2-treatment, 4-period, 2-sequence, crossover study, Active control

PKD13560	T1DM Germany (1 center) N=50	<ul style="list-style-type: none"> <li>- To demonstrate equivalence in exposure to insulin glargine given as HOE901-U300 test formulation T and HOE90-U300 reference formulation R in steady state conditions after 6 once-daily SC doses of 0.4 U/kg using the euglycemic clamp technique</li> <li>-To assess relative pharmacodynamic (PD) activity of the HOE901-U300 test formulation T to the HOE901-U300 reference formulation R in steady state conditions after 6 once-daily SC doses of 0.4 U/kg.</li> <li>-To assess the safety and tolerability of the test and reference formulations of HOE901-U300</li> </ul>	Double-blind, randomized, 2- treatment, 2- period, 2- sequence, crossover bioequivalence study
<b>Reports of Human Pharmacodynamic (PD) Studies</b>			
PKD11627	T1DM Germany (1 center) N=24	<ul style="list-style-type: none"> <li>-To assess the metabolic effect ratios of 3 different HOE901-U300 doses versus 0.4 U/kg of Lantus</li> <li>-To assess the exposure ratios and to compare the duration of action of 3 different HOE901- U300 doses versus 0.4 U/kg of Lantus</li> <li>-To explore the dose response and dose exposure relationship of HOE901- U300</li> <li>-To assess the safety and tolerability of HOE901- U300</li> </ul>	Randomized, double blind, 4 treatments, 4 periods and 4 sequences cross-over, using the euglycemic clamp technique Active control
PKD12270	T1DM Japan (1 center) N=18	<ul style="list-style-type: none"> <li>- To compare the metabolic effect of 2 different HOE901-U300 doses versus 0.4 U/kg Lantus</li> <li>-To compare the pharmacokinetic profile, duration of action of 2 different HOE901-U300 doses versus 0.4 U/kg Lantus</li> <li>-To explore the dose response and dose exposure relationship of HOE901-U300</li> <li>-To assess safety and tolerability of HOE901-U300</li> </ul>	Randomized, double blind, 3-sequence, 3 treatment, 3- period cross-over, single-dose study, using the euglycemic clamp technique Active control
PDY12335	T1DM Japan (1 center) N=20	<ul style="list-style-type: none"> <li>- To compare the 24-hour glycemic profile in continuous glucose monitoring of HOE901-U300 to Lantus at steady state</li> <li>-To compare between the 2 treatments :the change of fasting plasma glucose (FPG), self- monitored plasma glucose (SMPG), and postprandial plasma glucose (PPG); the efficacy on glycemic control in glycemic parameters; the occurrence of hypoglycemia</li> <li>-To assess the safety and tolerability of HOE901-U300</li> </ul>	Randomized, open-label, 2-treatment, 2- period 2-sequence, cross-over, multiple dose study Active control
TDR11626	T1DM Germany (1 center) N=30	<ul style="list-style-type: none"> <li>- To assess the safety and tolerability of 2 dose levels of HOE901-U300 in a once-daily multiple dosing regimen</li> <li>-To compare the PK and PD properties of 2 dose levels of HOE901-U300 with 0.4 U/kg Lantus in a once-daily multiple dosing regimen</li> </ul>	Randomized, double blind, 2-treatment, 2-period, 2- sequence, cross-over, 2 parallel cohort, euglycemic clamp study
<b>Phase 3 Studies assessing efficacy and safety</b>			
EFC12449	T1DM Japan (22 centers)	<ul style="list-style-type: none"> <li>- To compare the efficacy of HOE901-U300 and Lantus in terms of change of HbA1c from baseline to endpoint</li> </ul>	Randomized, open-label, 2-arm parallel-group

	N=243	<ul style="list-style-type: none"> <li>-To compare HOE901 U300 and Lantus in terms of: <ul style="list-style-type: none"> <li>-change from baseline to endpoint in fasting plasma glucose</li> <li>-pre-basal insulin injection plasma glucose,</li> <li>-variability of pre-basal insulin injection plasma glucose</li> <li>-8 point SMPG profile</li> <li>-reaching target HbA1c values</li> <li>-occurrence of hypoglycemia;</li> <li>-treatment satisfaction</li> </ul> </li> <li>-To assess safety and tolerability (including AIA)</li> </ul>	multicenter trial Active control
EFC12512	T2DM Japan (22 centers) N=241	<ul style="list-style-type: none"> <li>- To compare the efficacy of HOE901-U300 and Lantus in terms of change of HbA1c from baseline to endpoint when given as basal insulin in a regimen with oral antihyperglycemic drugs</li> <li>-To compare HOE901 U300 and Lantus in terms of: <ul style="list-style-type: none"> <li>-change from baseline to endpoint in fasting plasma glucose</li> <li>-pre-basal insulin injection plasma glucose,</li> <li>-variability of pre-basal insulin injection plasma glucose</li> <li>-8 point SMPG profile</li> <li>-reaching target HbA1c values</li> <li>-occurrence of hypoglycemia;</li> <li>-treatment satisfaction</li> </ul> </li> <li>-To assess safety and tolerability (including AIA)</li> </ul>	Randomized, open-label, 2-arm parallel-group multicenter trial Active control

## 5.2 Review Strategy

The content of this review critically evaluates the efficacy findings from the four pivotal phase 3 studies listed in Table 2. I reviewed efficacy data from the pivotal phase 3 trials individually instead of conducting an integrated summary of efficacy because of the differing trial designs and study populations within each trial. However, since there was some overlap in the trial design, objectives, and dosing regimens among all four pivotal trials, the reviewer created a section titled: “Common elements among 4 pivotal studies.” Unique characteristics of each pivotal trial were addressed in Section 5.3.

The review of safety, in addition to the four phase 3 trials, also included review of a 16-week phase 2 study (PDY12777).

Review of substudy EFC11628 and substudy EFC11629 are located in section 7.4.5 Special Safety Studies/Clinical Trials. These substudies were reviewed separately from the main efficacy studies because they were not designed to evaluate the efficacy of HOE901-U300; they were designed to evaluate adaptable dosing of HOE901-U300.

The reviewer used the information presented by the Sponsor in the Clinical Study Report (CSR), for each individual study, in addition to the Integrated Summary of Safety (ISS). Issues and concerns identified from the clinical summaries were addressed by in-depth review of the

submitted narratives and datasets. The reviewer evaluated all submitted narratives of deaths and nonfatal serious adverse events.

### 5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor submitted four new phase 3 trials as evidence of efficacy: one type 1 diabetes study (EFC12456) and three type 2 diabetes studies (EFC11628, EFC11629, EFC12347). In this section of the review, I discuss the common elements shared among pivotal trials under the heading of “Common elements among 4 pivotal studies.” Under this heading, the following factors are discussed:

1. Common characteristics
2. Inclusion and exclusion criteria for pivotal studies
3. Commonalities in dosing
4. Commonalities of safety analysis

At the conclusion of this Common element section, I discuss each trial separately emphasizing each trial’s unique characteristics.

For discussion of substudies supporting the adaptable dosing regimen, refer to section 7.4.5 *Special Safety Studies/Clinical Trials*.

#### Common elements among 4 pivotal studies

The four pivotal trials had similarities in their trial design, primary objectives, methodology of starting IMP (investigational medicinal product) dosing, use of insulin pens, and dose adjustments. See Table 5 for details on common characteristics.

**Table 5 - Common characteristics among all pivotal studies (EFC12456, EFC11628, EFC11629, and EFC12347)**

Category	Description
Location	Multinational, multicenter
Design	Open-label, centrally randomized, active-comparator, parallel group studies
Blinding	Blinding of Investigators and patients was not possible as the injection volume of HOE901-U300 is one-third that of Lantus for the same dose
Comparator	Lantus (insulin glargine 100 U/mL)
Randomization	1:1 (Lantus: HOE901-U300)
Stratification of randomization	By screening HbA1c (<8.0% versus ≥8.0%),
Duration	6-month main study period followed by a 6-month controlled safety extension period
Primary objective	To show noninferiority of HOE901-U300 versus Lantus based on the change in HbA1c from baseline to endpoint at Month 6 with a noninferiority margin of 0.4% HbA1c
Primary efficacy variable	Change from baseline in HbA1c
Planned method for primary	Last Observation Carried Forward ( <b>LOCF</b> ): EFC11628 and

efficacy analysis*	EFC11629 Mixed Model for Repeated Measurements (MMRM): EFC12456 and EFC12347
Efficacy population: Modified intent-to-treat population	All randomized patients who received at least one dose of the IMP <b>and</b> had: <ol style="list-style-type: none"> <li>1. baseline assessment</li> <li><b>and</b></li> <li>2. at least one post-baseline assessment of any primary or secondary efficacy variables</li> </ol> Patients were analyzed for the treatment they were randomized to
Safety population	All patients randomized and exposed to at least one dose of IMP, regardless of the amount of treatment administered
Glucometer used	MyGlucoHealth (EFC11628 and EFC11629) Accu-Chek Aviva/Performa/Performa Nano (EFC12347 and EFC12456)
Insulin delivery	Pen device (see below for details)
*Method for handling of missing data was changed to MMRM from LOCF based on recommendation from FDA after studies 11628 and 11629 were already conducted	

Commonalities in main secondary endpoints are specified below. Differences between individual studies are also noted when pertinent.

Main secondary efficacy endpoints in the pivotal studies (except EFC12456 where no main secondary efficacy endpoints were defined) were:

- Incidence (%) of patients with at least 1 nocturnal hypoglycemia indicated as severe and/or confirmed by plasma glucose  $\leq 3.9$  mmol/L ( $\leq 70$ mg/dL) that occurred between 00:00 and 05:59 hours, from start of Week 9 to Month 6;
- Change in pre-injection SMPG (obtained within 30 minutes prior to injection of study drug; mean over last 7 days values) from baseline to endpoint (Month 6);
- Change in variability of pre-injection SMPG (obtained within 30 minutes prior to injection of study drug; coefficient of variation of measurements taken over the previous 7 days from baseline to endpoint (Month 6) for EFC11628, EFC11629, and EFC12456; variability of pre-injection SMPG at endpoint (Month 6) for EFC12347, because the variability of the pre-injection SMPG at baseline cannot be calculated as the pre-injection SMPG is measured only once before the first IMP injection.

Other secondary efficacy endpoints in the pivotal studies were:

- Proportion (%) of patients with HbA<sub>1c</sub> <7%
  - at Month 6;
  - at Month 6 having experienced no hypoglycemia event, indicated as severe and/or confirmed by plasma glucose < 3.0 mmol/L (54 mg/dL) that occurred during the last 3 months of the main 6-month on-treatment period;
  - at Month 6 having experienced no nocturnal hypoglycemia event, indicated as severe and/or confirmed by plasma glucose < 3.0 mmol/L (54 mg/dL) that occurred between 00:00 and 05:59 hours during the last 3 months of the main 6-month on-treatment period.

- Change in centrally measured FPG from baseline to endpoint (Month 6);
- Change in 8-point SMPG (mmol/L) profiles per time point from baseline to endpoint (Month 6) including change of nocturnal SMPG;
- Change in mean 24-hour plasma glucose from baseline to endpoint (Month 6);
- Change in variability of mean 24-hour plasma glucose from baseline to endpoint (Month 6);
- Change in daily basal insulin dose (U and U/kg body weight) from baseline to endpoint (Month 6);
- Change in total (basal plus mealtime) daily insulin dose (U and U/kg body weight) from baseline to endpoint (Month 6) in EFC11628 and EFC12456;
- Ratio of daily average basal/total insulin doses at baseline, Week 12, and endpoint (Month 6) in EFC11628 and EFC12456 studies;
- Proportion of patients with rescue therapy during the main 6-month on-treatment period for EFC11629 and EFC12347;

**Reviewer's comment: The 12 month treatment duration of the HOE901-U300 program was chosen to obtain long term efficacy and safety data. Use of the 6-month treatment duration to establish efficacy of a new insulin product is acceptable. The open label design is not uncommon in insulin trials, and acceptable in the case of HOE901-U300 (given the differences in volume between HOE901-U300 vs. Lantus).**

Commonalities in key inclusion and exclusion criteria for pivotal studies:

*Inclusion Criteria:*

- Adult >18 years old, male and non-pregnant female, patients with DM

*Exclusion Criteria:*

- weight change of  $\geq 5$  kg during the last 3 months prior to screening visit
- latest eye examination by an ophthalmologist (US/Canada: ophthalmologist or optometrist) >12 months prior to randomization
- unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema
- uncontrolled or severe organ failure including: end stage renal disease (modification of diet in renal disease [MDRD]) <15 mL/min or on renal replacement treatment), hemoglobinopathy or hemolytic anemia, hypertension ([SBP]>180 mmHg and/or diastolic blood pressure [DBP] >95 mmHg at screening); Myocardial infarction, stroke, or heart failure in the past 3 months; hepatic, gastrointestinal cardiovascular, respiratory, neurological, psychiatric, active malignant tumor or other major systemic disease that might interfere with the evaluation of study medication according to Investigator's medical judgment
- transfusion of blood or plasma products within 3 months prior to screening visit
- any clinically significant abnormality identified on physical examination, laboratory tests
- active liver disease or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times upper limit of normal or total bilirubin >1.5 times upper limit of normal (except in case of documented Gilbert's syndrome) at screening

- positive test for hepatitis B surface antigen and/or hepatitis C antibody at screening
- use of systemic glucocorticoids (excluding topical application or inhaled forms) for 1 week or more within 3 months prior to the time of screening
- night shift workers
- women of childbearing potential (premenopausal, not surgically sterile for at least 3 months prior to the time of screening) not using highly-effective (i.e., with low failure rate <1% per year) method(s) of birth control throughout the study and/or unwilling to be tested for pregnancy

**Reviewer’s comment: Inclusion and exclusion criteria and their rationale are acceptable. Exclusion criteria attempt to limit risk of patients and exclude patients with advanced comorbid conditions.**

Commonalities in Dosing

All protocols had pre-defined methodology of starting the IMP dose (see Table 6).

**Table 6 - Methodology of starting IMP dose among pivotal trials (EFC12456, EFC11628, EFC11629, and EFC12347)**

Basal insulin prior to randomization	Starting dose of HOE901-U300 or Lantus
<b>Once a day:</b> Lantus, NPH, Levemir	1:1 unit conversion of basal insulin dose, administered once daily
<b>Twice daily:</b> Levemir <sup>a</sup> , NPH	Total daily basal insulin dose x 80%, then administered once daily
None (Insulin naïve)	0.2 U/kg once daily

<sup>a</sup> in T1DM trial

**Reviewer’s comment: The algorithm used to convert between a commercial insulin product to IMP (or to begin insulin, in the case of insulin naïve patients) in the protocols was based on the approved Lantus label.** (b) (4)

[Redacted]

*Sanofi response: Based on the results of studies PKD11627 and TDR11626 it has been recommended in the phase 3 studies to convert from previous daily dose of Lantus U100 to HOE901-U300 without changing daily doses (i.e., change-over 1:1 unit-wise) with subsequent dose adjustment as needed depending on fasting plasma glucose. The results of these studies will be in the HOE901-U300 NDA.* (b) (4)

[Redacted]

All trials used insulin pen devices for administration of basal insulin. All trials used the SoloStar pen for administration of Lantus; however, the pen devices varied for administration of HOE901-U300. See Table 7 for details of pen devices used in pivotal trials.

**Table 7 - Pen characteristics used in pivotal trials**

Pen characteristics	SoloStar	Modified SoloStar	(b) (4)
Trials	all pivotal trials	EFC11628 EFC11629	EFC12347 EFC12456 (T1DM)
Insulin administered by pen	Lantus	HOE901-U300	HOE901-U300
Pen minimal to maximum single dose administration	1 U to 80 U	42 U to 180 U	3 U to 90 U
Minimum increment dose	1 U	3 U	1.5 U

IMP titration strategy varied by population being studied (T1DM vs. T2DM). Both goals and titration were more conservative in patients with T1DM. See Table 8 for details. Doses greater than the possible maximum single dose of the pen used were given as two or more consecutive SC injections at the same time with the daily dose split in equal or close to equal doses.

For EFC11628 and EFC11629, patients had to be on a minimum of 42 U of basal insulin. The reason for this dose was that at doses above 39 U, dosing accuracy was guaranteed for HOE901-U300 using the modified SoloStar as for the same doses of Lantus (when using the SoloStar).

Most protocols specified that efforts should be made to complete up-titration of basal insulin by 8 to 12 weeks post randomization, with the exception of EFC12456, which specified that target plasma glucose should be reached by 6-8 weeks post randomization.

Administration of insulin for all trials occurred once daily by deep subcutaneous injection, alternating between the left and right anterolateral, left, and right posterolateral abdominal wall or thighs or upper arms. Within a given area, the injection site was to be rotated at each time to prevent skin reactions at the injection site.

The time of basal insulin administration occurred in the evening in all T2DM trials, but was split as a fixed evening or fixed morning time in the T1DM trial.

Mealtime insulin doses (for the T1DM trial and the basal bolus T2DM trial) were to be adjusted to optimize glycemic control after basal insulin doses were optimized. Titration of mealtime insulin was done at the Investigator's discretion. The Sponsor did not provide investigators a meal time titration algorithm.

**Table 8 - Titration of basal insulin used in pivotal trials (EFC12456, EFC11628, EFC11629, and EFC12347)**

	Type 1 DM trials EFC12456	Type 2 DM trials (EFC12347, EFC11628, EFC11629)
Basal dose adjustment frequency	Once weekly, no more frequently than every 3 to 4 days depending on pre-breakfast SMPG	
Goal pre-breakfast SMPG	80 to 130 mg/dL	80 to 100 mg/dL
Dose titration to meet goal	Increase basal insulin dose by $\geq 10\%$ , not exceeding 4.5 U for HOE901-U300 or 4 U for Lantus per dose increase	Insulin dose increase for pre-breakfast SMPG:  100 to 140 mg/dL: +3 U $\geq 140$ mg/dL: +6 U $\geq 60$ to $< 80$ mg/dL: -3 U $< 60$ mg/dL: -3U
Time of basal insulin administration	Split between -once daily evening <sup>a</sup> -once daily morning <sup>b</sup>	Once daily in evening <sup>a</sup>
Titration monitoring team monitored the titration process in all 4 Phase 3 studies. For titration issues an external Insulin-Dosing Supervision Committee (IDSC) consisting of 2 external expert diabetologists reviewed data and provided recommendations. The IDSC focused on titration of the IMP.		
<sup>a</sup> Defined as the time period the time immediately before dinner to bedtime.		
<sup>b</sup> Defined as the time period between pre-breakfast and pre-lunch		

In general, patients continued their prior background therapy as concomitant antidiabetic medication. See Table 9 below for details.

**Table 9 – Prior and concomitant antidiabetic medications**

<i>Study</i>	<i>Prior basal insulin</i>	<i>Other antidiabetic therapy</i>
EFC12456	>at least 1 year of basal insulin (glargine, NPH, Levemir)	Mealtime insulin (glulisine, aspart or lispro)
EFC11628*	>at least 1 year of basal insulin (glargine or NPH)	Mealtime insulin (glulisine, aspart or lispro) +/- metformin
EFC11629*	>at least 6 months of basal insulin (glargine or NPH)	Oral antihyperglycemic agents (AHA) excluding sulfonylureas
EFC12347*	insulin naive	Non-insulin antihyperglycemic agents (sulfonylurea, glinides and/or AHA not approved for combination with insulin stopped at baseline but patients also had to be taking another non-insulin AHA permitted as background therapy during the study)
*other non-insulin therapy was continued as NIMP except as noted		

Source: Table 4, Summary of Clinical Efficacy

Statistical methodology

**Primary endpoint:**

The primary efficacy endpoint and assessment was the same in all four pivotal trials (except for handling of missing data as noted) and was shown in Table 5.

- Noninferiority of HOE901-U300 vs. Lantus had to be demonstrated (primary endpoint). 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 non-inferiority margin of 0.4% HbA1c. 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%.

**Secondary endpoints:**

All 3 T2DM trials used a hierarchical testing strategy to evaluate the main secondary endpoints. *The first main secondary endpoint, evaluating the superiority of HOE901-U300 over Lantus in incidence of patients with at least one nocturnal hypoglycemia event, also applies to study EFC12456 (for the Overall HOE901-U300 and the Overall Lantus groups).*

If the primary endpoint listed above was met, then to control for type I error, a hierarchical step-down testing procedure was applied as follows: (The tests stop as soon as an endpoint is found not statistically significant at one-sided  $\alpha = 0.025$  level)

1. Superiority of HOE901-U300 over Lantus in incidence of patients with at least one nocturnal hypoglycemia between start of week 9 and endpoint (month 6) that occurred between 00:000 and 05:59 hours, indicated as severe and/or confirmed by plasma glucose  $\leq 70$  mg/dL (3.9 mmol/L),
2. Superiority of HOE901-U300 over Lantus in change in pre-injection plasma glucose from baseline to endpoint (month 6)
3. Superiority of HOE901-U300 over Lantus in change in variability of pre-injection plasma glucose from baseline to endpoint (month 6).

As noted above, the percentage of patients experiencing at least one nocturnal hypoglycemia was evaluated from the time period of **start of Week 9 to Month 6**. Therefore, the time period between Baseline and Week 8 was excluded from this secondary efficacy analysis.

**Reviewer's comment: The FDA has expressed concern to the Sponsor** (b) (4)

**In a communication with the Sponsor on May 3, 2012, the FDA state** (b) (4)

### Commonalities in safety analysis

Safety results were analyzed in all trials by treatment group (HOE901-U300 or Lantus) for the following:

- Hypoglycemia (symptomatic, asymptomatic, severe, probable, relative);
- Local tolerability at injection site reactions;
- Other adverse events and serious adverse events;
- Vital signs, including blood pressure and heart rate measures;
- Body weight;
- Physical examination;
- 12-lead EKG;
- Cardiovascular events;
- Safety laboratory tests that were processed by a central laboratory;
- Immunogenicity (analyses of AIA)

### Severe Hypoglycemia Review Board

All hypoglycemic events reported by the Investigator as severe and/or reported as SAEs, were retrospectively and independently reviewed under blinded conditions. The results of this classification were not available in the database at the time of the first database lock.

### **Review of individual pivotal trials**

#### T1DM

##### **1. Study EFC12456**

Title: A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period

Sites: 12 countries: Canada, Czech Republic, Denmark, Estonia, Finland, Hungary, Japan, Latvia, Netherlands, Romania, Sweden, and USA.

Dates conducted: 12 September 2012 to 11 September 2013

Design: 6-month, multicenter, multinational, open-label, randomized, 4-arm parallel-group study comparing the efficacy and safety of HOE901-U300 and Lantus in patients with T1DM who had been on a basal plus mealtime insulin regimen for at least 1 year, with a 6-month safety extension period.

Subjects were randomized by 1:1:1:1 ratio to either HOE901-U300 or Lantus as a morning or evening injection, stratified by screening visit HbA<sub>1c</sub> (<8.0% versus ≥8.0%) and geographical region (Non-Japan; Japan).

**Reviewer's comments: The randomization of patients to morning injection times was in agreement with the Pre-IND communication, where the Agency recommended that the Sponsor evaluate time points other than the evening.**

See section *Common elements among 4 pivotal studies* section for other shared details regarding design and inclusion/exclusion criteria. Exclusion criteria specific to study EFC12456 are listed below. See protocol for a list of all inclusion/exclusion criteria.

Subjects:

*Exclusion Criteria:*

- HbA<sub>1c</sub> <7.0% or >10% at screening
- <1 year on any basal plus mealtime insulin and self-measured plasma glucose, (SMPG) before screening visit
- Patients not on stable insulin dose (±20% total basal insulin dose) in the last 30 days prior to screening visit
- Severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before screening visit
- Patients using premix insulins, human regular insulin as mealtime insulin and/or any glucose-lowering drugs other than basal insulin and mealtime analog insulin in the last 3 months prior to screening visit
- Use of an insulin pump in the last 6 months before screening visit and no plan to switch to insulin pump in the next 12 months;

**Reviewer's comment: Exclusion of patients with advanced presentations of diabetes (for example, patients with a history of severe hypoglycemia) is appropriate. In these patients, ADA targets of HbA<sub>1c</sub> are less stringent, with a goal of (<8%)<sup>1</sup>.**

Study Procedures and Visits:

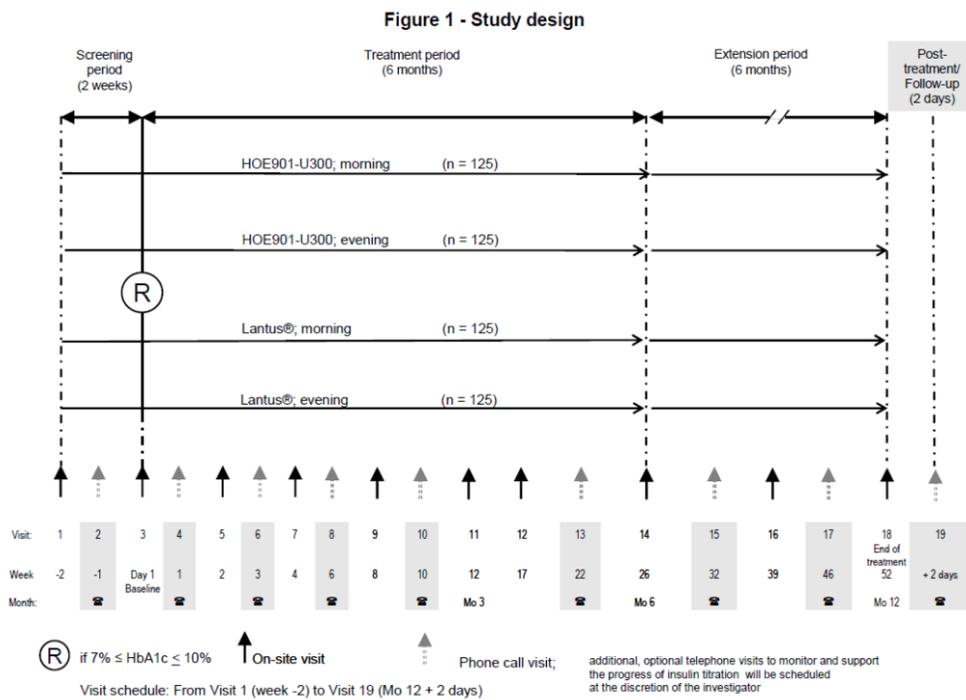
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<sup>1</sup> doi: 10.2337/dc14-S014 *Diabetes Care* January 2014 vol. 37 no. Supplement 1 S14-S80

The study consisted of a combination of mandatory 10 on-site visits and 9 mandatory telephone visits. In total, there were 2 screening, 12 treatment, 4 extension period, and 1 post treatment follow up visits (see Figure 4).

- Screening period (2 weeks) - consists of the screening visit and a telephone visit
  - Eligibility was determined, received equipment/training to measure and record SMPG.
- Treatment period (6 months) and Extension period (6 months) - Patients received HOE901-U300 or Lantus titrated to glycemic goals as well as lifestyle and diet counseling. Safety bloodwork, HbA1c, and fasting plasma glucose were obtained as well as reports of AE/SAEs and hypoglycemia.
- Extension period: both treatment groups continued their short-acting mealtime insulin analog and self-monitored plasma glucose (SMPG).
- Post-treatment/Follow-up (2 to 4 days after permanent drug discontinuation)-phone call or on-site visit if adverse event reported.

**Figure 4 - EFC12456 - Study Design**



Source: Study CSR, Figure 1

**Insulin Dosing and Titration:**

See also section: *Common elements among 4 pivotal studies* for details.

**Dose selection:**

- Before randomization, the total basal insulin dose of non-study drug at baseline visit (Visit 3) and the median of the fasting SMPG values in the last 3 days were used to calculate the starting dose of HOE901-U300 or Lantus.

Time of administration selection:

- IMP was injected subcutaneously once daily, at a fixed time for the duration of the study. Injection time could vary by  $\pm 1$  hour and was randomized either in the morning (period between pre-breakfast and pre-lunch), or evening (period immediately prior to the evening meal until bedtime), with the first IMP to occur on the day of randomization (baseline Visit 3) or the next day depending on the prior insulin regimen

Dose adjustments are discussed in Table 8 of the *Common elements among 4 pivotal studies* section. Upward titration of IMP was stopped for 1 week after a case of severe hypoglycemia (requiring third party assistance) or for an SMPG  $< 60$  mg/dL at the discretion of the Investigator, unless there was an adequate explanation (e.g., omission of a meal or heavy exercise).

Patients continued to use their pre-study short-acting mealtime (bolus) insulin analog (glulisine, aspart, or lispro) during the study. These short-acting mealtime insulins were considered non-investigational medicinal product (NIMP). Regular human insulin was not permitted as mealtime insulin.

Mealtime insulin analog adjustments occurred at the Investigator's discretion using data from: 5-point SMPG, 2-hour postprandial plasma glucose and carbohydrate content of the meal. Mealtime insulin titration goal was to reach a 2-hour postprandial SMPG of  $< 8.9$  mmol/L (160 mg/dL) while avoiding hypoglycemia. For the purpose of this protocol, 2 hours postprandial was defined as 2 hours after the start of the meal. Mealtime insulin was injected at different sites than the IMP injection site.

Endpoints:

*Primary efficacy endpoint*

- See section *Common elements among 4 pivotal studies/table 7*

*Secondary efficacy endpoints*

-See section *Common elements among 4 pivotal studies*

*Safety*

-See section *Common elements among 4 pivotal studies*

Statistical Methods:

Although, patients were randomized by 1:1:1:1 ratio to HOE901-U300 or Lantus as a morning or evening injection, they were evaluated as **overall** (morning + evening) HOE901-U300 to **overall** (morning + evening) Lantus, in efficacy analyses. The analysis of the overall HOE901-U300 and overall Lantus group was prespecified in the SAP of the study.

The primary efficacy variable (change in HbA1c from baseline to endpoint in %) was analyzed using a Mixed Model with Repeated Measurements (MMRM) approach, under the missing at random framework carried out via PROC MIXED using an adequate contrast at visit 14 [month 6, week 26]). This model included fixed categorical effect factors for randomized group, visit,

randomized group -by-visit interaction, randomization strata of screening HbA1c (<8.0, ≥8.0%), randomization strata of geographical region (Non-Japan; Japan), as well as, the continuous fixed covariates baseline HbA1c and baseline HbA1c-by-visit interaction.

The Sponsor defined the main 6-month on-treatment period for efficacy as the time from the first injection of IMP up to Month 6 (Visit 14) or up to 2 days (1 day for FPG, SMPG; 0 day for insulin dose) after the last injection of IMP if discontinued within this period, whichever was earlier for the patient. For efficacy analyses, “baseline” was defined as the last available value prior to the first dose of IMP. If a patient discontinued the treatment prematurely during the main 6-month on-treatment period, the time windows described in Table 10 were applied to retrieve assessments performed at the end of treatment visit for the MMRM analysis. These analysis windows in Table 10 were used for continuous efficacy endpoints (including HbA1c). For categorical efficacy endpoints, patients with missing assessment at month 6 were considered as non-responders in the analysis.

**Table 10 - Analysis windows definition**

Time point	Targeted study day	Analysis window in study days
Week 12	85	57 to 112
Week 26	183	155 to 210

Study days are calculated from the day of first IMP injection; the day of first IMP injection being Day 1.

Source: EFC12456 SAP table 3

*Multiplicity issues:*

The Sponsor selected a hierarchical step-down testing procedure to control the type I error for the primary endpoint only (**not** for secondary endpoints, in contrast to the other pivotal studies). Only if non-inferiority of HOE901-U300 in change in HbA1c from baseline to endpoint versus Lantus has been demonstrated, then superiority of HOE901-U300 overall over Lantus overall was tested for the primary endpoint. The superiority of HOE901-U300 over Lantus Overall was to be 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 Overall and Lantus Overall on mITT population is < 0 (zero). The tests for the primary endpoint (month 6, week 26) are performed one-sided at level  $\alpha = 0.025$ .

No statistical test is performed for secondary/exploratory endpoints in regards to multiplicity issues (in contrast to the T2DM trials).

*Sample size calculation:*

The sample size was chosen to ensure sufficient power only for the primary efficacy analysis of HbA1c change from baseline to endpoint (month 6). Sample size was 500 patients, (125 in each group): HOE901-U300 (morning or evening) or Lantus (morning or evening) injection. This sample size ensured that the upper confidence limit of the two-sided 95% CI for the mean overall

difference between HOE901-U300 and Lantus would not exceed 0.4% HbA1c with >99% power assuming that SD is 1.0% assuming that all patients will be evaluable.

### T2DM (3 pivotal studies)

## **2. Study EFC11628- T2DM Basal/bolus insulin therapy**

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period

Sites: Multinational, multicenter (180 centers in 13 countries). Countries included Canada, Czech Republic, Estonia, Finland, France, Germany, Hungary, Latvia, Mexico, Netherlands, Romania, South Africa, and United States.

Dates conducted: 28 December 2011 to 30 January 2013

Design: This was a 6-month, multicenter, randomized, open-label, parallel-group study comparing HOE901-U300 to Lantus while maintaining meal time insulin, with a 6-month comparative safety extension period, and a follow-up on-site visit 4 weeks post-treatment. Patients were randomized to HOE901-U300 or Lantus using a randomization ratio of 1:1.

See section *Common elements among 4 pivotal studies* for other shared details regarding design and inclusion/exclusion criteria. Exclusion criteria specific to study EFC11628 are listed below. See protocol for a list of all inclusion/exclusion criteria.

### Subjects:

#### *Exclusion Criteria:*

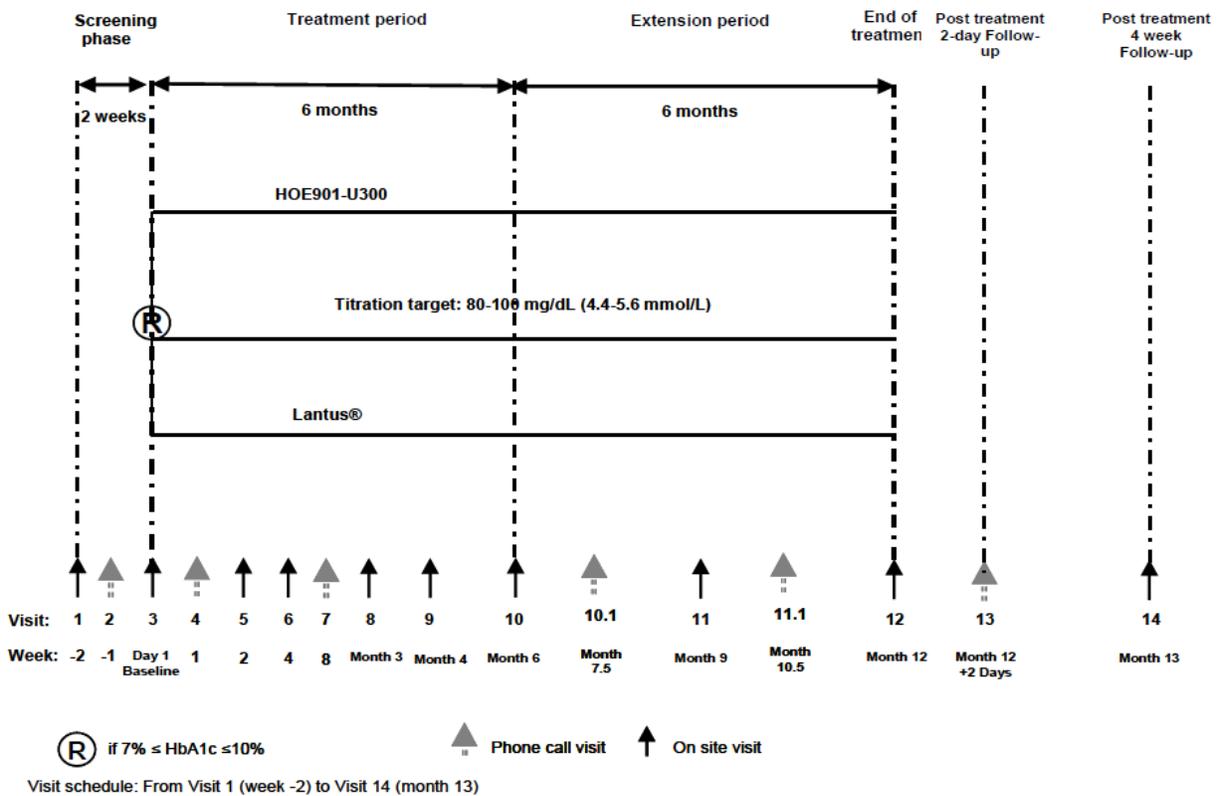
- HbA1c <7.0% or >10% at screening
- diabetes other than type 2 diabetes mellitus
- hypoglycemia unawareness or hospitalization for diabetic ketoacidosis during the previous 6 months
- less than 1 year on basal plus mealtime insulin and self-monitoring of blood glucose;
- patients using premix insulins or basal insulins other than insulin glargine or NPH and patients using any non-insulin antihyperglycemic drugs other than metformin in the last 3 months before screening visit
- total daily dose insulin glargine <42 U or equivalent dose of NPH in the last 4 weeks prior to the study (if NPH is used as basal insulin prior to the study)
- patients using human regular insulin as mealtime insulin in the last 3 months before screening visit
- use of insulin pump in the last 6 months before screening visit
- initiation of new glucose-lowering medications in the last 3 months before screening visit

### Study Procedures and Visits:

The study consisted of 14 visits (either phone call or on site). Phone call visits were planned at V2 (week -1), V4 (week 1), V7 (month 2) and V13 (month 12 + 2 days). Diet and lifestyle counseling was to occur throughout study visits. See figure 6.

- Screening phase (up to 2 weeks)- Visit 1 and Visit 2
  - Informed consent, demography, medical/surgical history, documentation of type 2 diabetes history/medications/comorbidities, and a physical exam are obtained.
  - Blood work is analyzed at a central laboratory for HbA1c, safety labs, Hepatitis B surface antigen, Hepatitis C Ab, serum pregnancy test, FSH, and estradiol in menopausal women.
  - Instructions on and administration of glucometer and e-diary use are provided.
- Treatment period (6 months) (Visit 3- Day 1 until Visit 10, month 6)
  - Patients, who successfully meet inclusion criteria and have no exclusion criteria, are randomized in a 1:1 ratio to HOE901-U300 or Lantus. Basal insulin was administered at an individually titrated dose once daily in the evening. Safety bloodwork, HbA1c, and fasting plasma glucose are obtained as well as reports of AE/SAEs and hypoglycemia.
- Extension period (6 months), (Visit 11- month 9 until Visit 12, month 12)
  - Patients continue IMP for an additional 6 months.
- A follow-up with a safety visit by phone contact 2 days (up to 4 days) after the end of treatment visit
  - Patients were assessed for any new medical event, disease, change in medications, AE/SAEs since last visit
- A final follow-up on-site visit, 4 weeks after the end of treatment visit

**Figure 5 - EFC11628 - Study design**



Source: Figure 1, CSR

Insulin Dosing and Titration: See *Common elements among 4 pivotal studies* for dosing and titration details shared among all studies.

Starting dose of IMP: All participants enrolled in EFC11628 were taking a minimal basal dose of 42 U prior to start of trial. Basal insulin dose (either HOE901-U300 or Lantus) had to be divisible by 3. If dose was not divisible by 3, the dose was rounded down to the next lower number divisible by 3.

Endpoints:

*Primary efficacy endpoint*

-See section *Common elements among 4 pivotal studies*.

*Secondary efficacy endpoints:*

-See section *Common elements among 4 pivotal studies*

*Safety endpoints:*

-See section *Common elements among 4 pivotal studies*.

### Statistical Methods

**Both EFC11628 and EFC11629 used the same SAP. Unless specified, the following descriptions apply to both studies.**

The Sponsor defined the main 6-month on-treatment period for efficacy as the time from the first injection of IMP up to Month 6 (Visit 10), or up to 2 days (1 day for FPG, SMPG; 0 day for insulin dose) after the last injection of IMP if discontinued within this period or up to the introduction of the rescue therapy (for EFC11629 only), whichever was earlier for the patients. For efficacy analyses, “baseline” was defined as the last available value prior to the first dose of IMP.

The primary efficacy variable (change in HbA1c from baseline to endpoint in %) was analyzed 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. Differences between HOE901-U300 and Lantus and two-sided 95% confidence intervals are estimated within the framework of ANCOVA.

If a patient discontinued the treatment prematurely, during the 6-month treatment period, or did not have any HbA1c value at endpoint (month 6), the last post-baseline on-treatment HbA1c measurement during the 6-month treatment period was to be used as the HbA1c value at month 6 (Last Observation Carried Forward [LOCF] procedure). In study EFC11629, for all patients rescued during the 6-month treatment period, the last post-baseline HbA1c measurement before the rescue and during 6-month on-treatment period is used as the HbA1c endpoint.

#### *Multiplicity issues:*

The Sponsor selected a hierarchical step-down testing procedure to control the type I error for the primary endpoint and for defined primary and secondary endpoints.

#### *To control for type I error in primary endpoint:*

Only if non-inferiority of HOE901-U300 versus Lantus has been demonstrated, step 2 tests 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 (zero).

See Common elements among 4 pivotal studies regarding control for Type 1 error for secondary endpoints.

#### Sample size calculation

A sample size of 800 patients (400 with HOE901-U300 and 400 with Lantus) will ensure that the upper confidence limit of the two-sided 95% CI for the mean difference between HOE901-U300 and Lantus would not exceed 0.4% HbA1c (upper noninferiority margin) with more than 99 % power assuming that standard deviation (SD) is 1.3% (modified intention-to-treat [mITT] population n = 800) that the true difference between HOE901-U300 and Lantus is zero in HbA1c and assuming that all patients will be evaluable.

### **3. Study EFC11629 - Type 2 DM background oral antidiabetes drugs**

Title: 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus both in combination with oral antihyperglycemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period

Sites: 213 centers in 13 countries (Canada, Chile, Finland, France, Germany, Hungary, Mexico, Portugal, Romania, Russia, South Africa, Spain, and United States)

Dates conducted: 14 December 2011 to 26 April 2013

Design:

This was a 6-month, multicenter, randomized, open-label, parallel-group study comparing HOE901-U300 and Lantus both plus oral antihyperglycemic drug(s) in patients with type 2 diabetes mellitus with a 6-month safety extension period.

See section *Common elements among 4 pivotal studies* section for other shared details regarding design and inclusion/exclusion criteria. Inclusion and exclusion criteria specific to study EFC11629 are listed below. See protocol for a list of all inclusion/exclusion criteria.

Subjects:

*Exclusion Criteria:*

- HbA<sub>1c</sub> <7.0% or >10% at screening;
- Less than 6 months on basal insulin treatment together with oral antihyperglycemic drug(s);
- Hypoglycemia unawareness or hospitalization for diabetic ketoacidosis during the previous 6 months;
- Use of premix insulins or basal insulins other than insulin glargine or NPH in the last 3 months before screening visit and patients using sulfonylurea in the last 2 months before screening visit;
- Total daily dose insulin glargine <42 U in the last 4 weeks prior to randomization or equivalent doses of NPH insulin (if NPH was used as basal insulin prior to study);
- Patients using mealtime insulin (short acting analog, human regular insulin) for more than 10 days in the last 3 months before screening visit;
- Use of an insulin pump in the last 6 months before screening visit

Concomitant diabetes therapy

Patients taking a stable dose of oral antihyperglycemic background therapy for 3 months were eligible to enroll except for those taking sulfonylureas, which are prohibited within 2 months before the screening visit and during participation in the study. The doses and combinations of oral antihyperglycemics were to be in accordance to the authorized local labeling, and were to be kept stable throughout the study unless there was a specific safety issue related to these treatments.

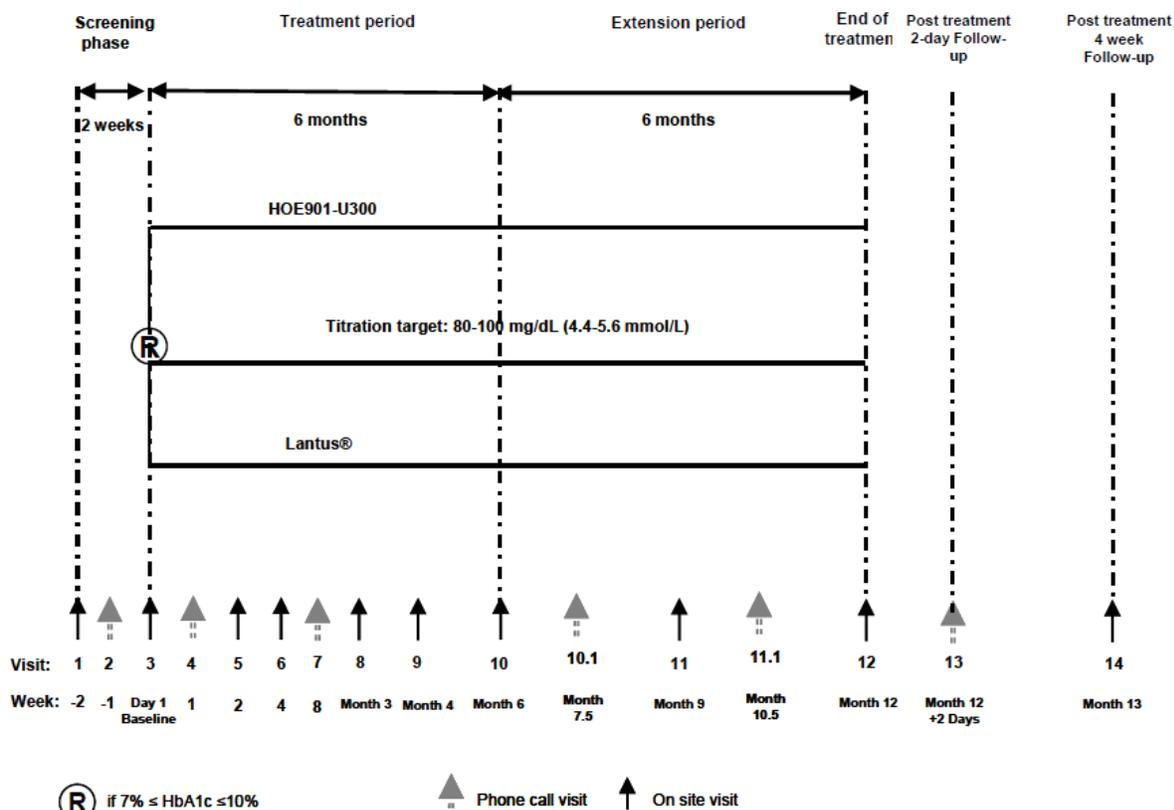
**Reviewer's comment: The co-administration of oral anti-diabetic drugs are in keeping with expected clinical practice and help inform the efficacy and safety of combined use.**

Study Procedures and Visits:

The study consisted of:

- A screening period (up to 2-weeks); (visit 1 and [phone] visit 2) where informed consent was obtained.
- A main 6-month treatment period (visit 3-day 1 to visit 10-month 6) comparing HOE901-U300 to Lantus while maintaining oral antihyperglycemic drug(s), except sulfonylureas (see above). Visits alternate between in-person visits and telephone visits with weekly titration of IMP, monitoring for any medical AE/SAEs, compliance, change in medical history, hypoglycemia, and evaluation of injection site and e-diary. Intermittent testing for safety labs occur during this period
- A 6-month non-voluntary comparative safety extension period during which patients maintained their study treatment and their background oral antihyperglycemic treatment. During this period, patients received life style and diet counseling (visit 11, month 9 to visit 12, month 12).
- A follow-up with a safety visit by phone contact 2 days (up to 4 days) after the end of treatment visit (this was the final follow up visit for patients who did not participate prior to Amendment 5);
- A final follow-up phone call, for all patients +2 to +4 days after IMP discontinuation, was performed to assess for AE/SAE, hypoglycemia or change in medical history. An on-site visit, (4 weeks after the end of treatment), was performed for patients who participated after enactment of Amendment 5 to protocol).

**Figure 6 - EFC11629 - Study design**



Visit schedule: From Visit 1 (week -2) to Visit 14 (month 13)

Source: Study CSR figure 1

### Insulin Dosing and Titration:

See section *Common elements among 4 pivotal studies* for dosing and titration information.

Dose initiation: In particular, for study EFC11629, the minimal daily dose of insulin was 42 units as either Lantus or HOE901-U300. If basal insulin dose was not divisible by 3, it had to be rounded down to the next lower number divisible by 3

### Rescue medication:

If FPG or HbA<sub>1c</sub> values were above the target values and no reasonable explanation existed, or if appropriate action failed to decrease FPG/HbA<sub>1c</sub> under the threshold values:

- Intensification of the treatment was considered after thorough evaluation of the patient's glycemic control and *not based on one value*.
  - Choice of the anti-diabetic treatment to be added to the basal insulin was based on Investigator's decision and local labeling documents. Adding prandial insulin could have been the preferred option.
  - All assessments for primary and secondary efficacy and safety parameters planned in the final on-treatment assessment visit (visit 12) were to be performed at a specific Pre-Rescue visit before adding the "rescue medication." Then the

patient continued the IMP and stayed in the study in order to collect safety information. The planned visits and assessments were to occur until the last scheduled visit.

- Short-time use (i.e., 10 consecutive days at maximum) of short-acting insulin (e.g., due to acute illness or surgery) was not considered as rescue therapy.

Endpoints:

Refer to Endpoints section in Study EFC11628. Both EFC11628 and EFC11629 shared the same SAP and have the same (with named exceptions above), endpoints (efficacy and safety), and statistical methods.

**4. Study EFC12347-Type 2DM (insulin naïve)**

Title: 6-month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycemic drugs with a 6-month Safety Extension Period

Sites:

Europe, Japan, and North America in 15 countries: (Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland, Hungary, Japan, Latvia, Lithuania, Romania, Slovakia, Sweden, The Netherlands, and United States).

Dates conducted: 31 August 2012 to 11 September 2013

Design: This was a multicenter, multinational, open-labeled, randomized, 2-arm parallel-group, comparative study. Patients were randomized 1:1 to HOE901-U300 or Lantus. Randomization was stratified according to HbA1c values at screening (<8.0%; ≥8.0%) and geographical region (non-Japan; Japan) with a minimum of 20% randomized patients per HbA1c strata.

See section *Common elements among 4 pivotal studies* section for other shared details regarding design and inclusion/exclusion criteria. Inclusion and exclusion criteria specific to study EFC12347 are listed below. See protocol for a list of all inclusion/exclusion criteria.

Subjects:

*Exclusion Criteria:*

- T2DM for less than 1 year duration
- HbA1c in the range of >11% and <7%
- History of hypoglycemia unawareness and/or diabetic ketoacidosis during the previous 6 months
- Not adequately controlled on stable doses of non-insulin antihyperglycemic drug(s)
- <6 months before screening with non-insulin antihyperglycemic treatment or dose change in previous 3 months
- Patients receiving sulfonylureas or glinides or drugs not approved for combination with insulins. (these drugs are to be discontinued at baseline)

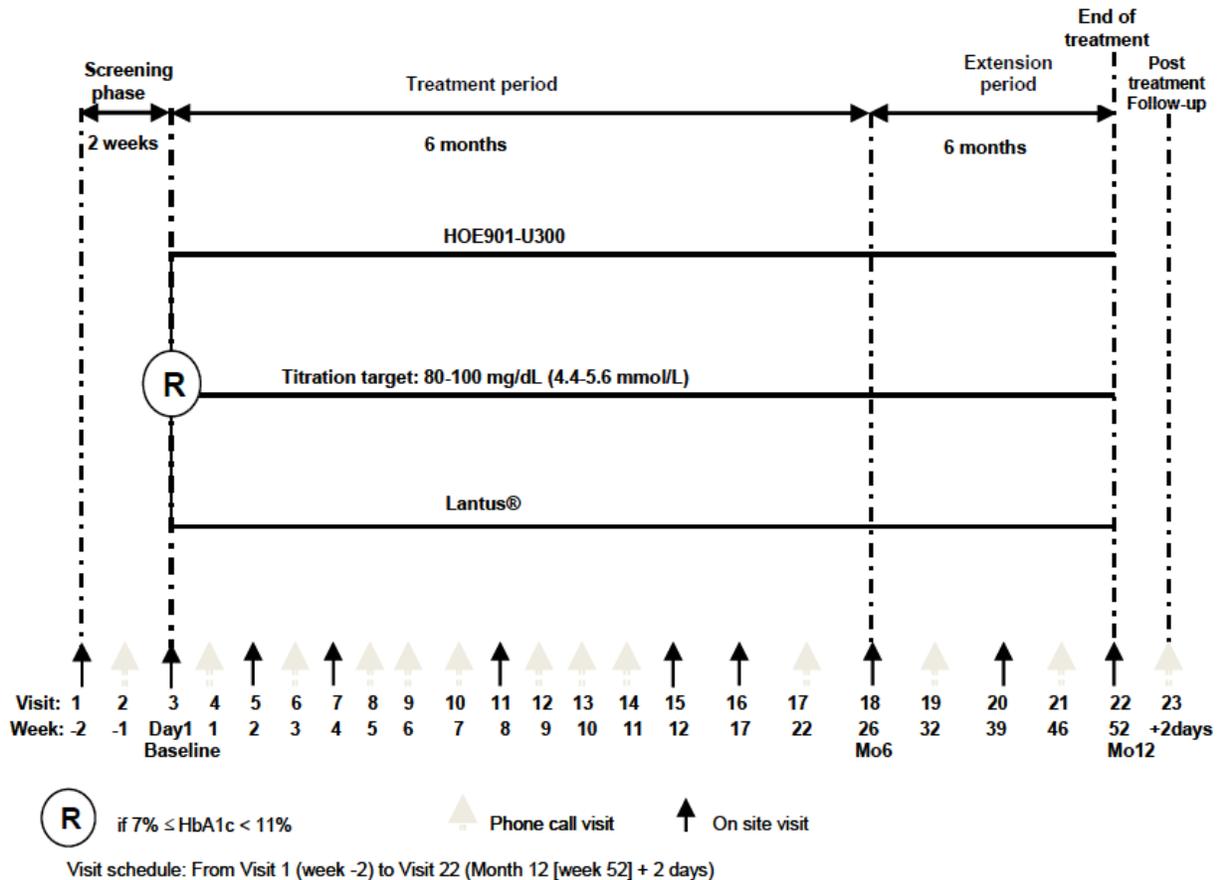
- Current or previous insulin use except for a maximum of 8 consecutive days during the last year prior to screening

Study Procedures and Visits:

Lifestyle and diet counseling was given by a site provider and was continued during the study.

- A screening period (up to 2-weeks); (visit 1 and [phone] visit 2) where informed consent, laboratory testing, physical examination, and training on use of glucometer and e-diary were performed.
- A main 6-month comparative efficacy and safety period (visit 3-day 1 to visit 18-month 6) while patients maintain use of oral antihyperglycemic drug(s). Visits during this period alternate between in-person visits and telephone visits. During these visits, titration of IMP continued weekly. Patients had monitoring for any medical AE/SAEs, compliance, change in medical history. Intermittent safety tests were performed.
- 6-month Safety extension period (V19 to visit 22, month 12- total of 4 visits) in which patients continued IMP.
- Post treatment Follow-up visit (V23, month 12 +2 days) occurred after the last administration of study IMP, post treatment follow up was scheduled +2 up to +4 days after permanent discontinuation of treatment. The patient was assessed for any new medical event, change in symptoms or new concomitant medications.

**Figure 7 - EFC12347 - Study design**



Source: Study CSR Figure 1

**Insulin Dosing and Titration:** Patients continued with their non-insulin antihyperglycemic drug(s) at stable doses with the exception of sulfonylureas, glinides and agents not approved in combination with insulin according to local labeling/local treatment guidelines that, if used, were discontinued at the start of the basal insulin.

**Basal insulin dose initiation:** The initial daily dose of basal insulin in both treatment groups (HOE901-U300 and Lantus), was 0.2 U/kg body weight rounded to the closets number divisible by 3.

**Reviewer’s comment:** The starting initial dose (0.2 U/kg) of basal insulin glargine in both treatment groups is in agreement with the Lantus label as a starting dose for insulin naive patients.

See *Common elements among 4 pivotal studies* regarding titration parameters

Rescue therapy

Rescue therapy was considered if FPG or HbA<sub>1c</sub> measurements were above the target values without a reasonable explanation, or if appropriate action failed to improve values, after the titration period (post Week 12). Initiation of rescue therapy was determined the Investigator and was based on an overall and thorough evaluation of the patient's glycemic control. Rescue therapy was started with a NIMP. All assessments for primary and secondary efficacy and safety parameters were performed before adding the "rescue medication." The patient continued the IMP and stayed in the study in order to collect safety information.

Short-time use (10 consecutive days at maximum) of short-acting insulin (e.g., due to acute illness or surgery) was not considered as rescue therapy.

#### Endpoints:

##### *Efficacy*

See section Common elements among 4 pivotal studies

##### *Secondary efficacy endpoints*

See section Common elements among 4 pivotal studies

##### *Safety*

See *Common elements among 4 pivotal studies* for safety endpoints.

#### Statistical Methods:

The primary efficacy variable (change in HbA<sub>1c</sub> from baseline to endpoint in %) was analyzed using a Mixed-effect Model with Repeated Measures (MMRM) approach, under the missing at random framework carried out via PROC MIXED using an adequate contrast at visit 18 [month 6, week 26]). The model includes fixed categorical effects of treatment group, visit, treatment-by-visit interaction, randomization strata of screening HbA<sub>1c</sub> (<8.0, ≥8.0%), randomization strata of geographical region (Non-Japan; Japan), as well as, the continuous fixed covariates of baseline HbA<sub>1c</sub> value and baseline HbA<sub>1c</sub> value-by-visit interaction. The treatment group has two levels (HOE901-U300 and Lantus) and the visit factor (with nominal visits) has two levels (visit 15 [week 12] and visit 18 [week 26, month 6]).

##### *Multiplicity issues:*

The Sponsor selected a hierarchical step-down testing procedure to control the type I error for the primary endpoint and for defined secondary endpoints.

##### *To control for type I error in primary endpoint:*

Only if non-inferiority of HOE901-U300 versus Lantus was demonstrated for the primary outcome, then testing of superiority of HOE901-U300 over Lantus was performed. 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 HbA<sub>1c</sub> from baseline to endpoint between HOE901-U300 and Lantus on mITT population is < 0 (zero).

*To control for type I error for secondary endpoints, a hierarchical step-down testing procedure was applied*

See *Common elements among 4 pivotal studies* for details regarding controlling for type 1 error.

*Sample size:*

In consideration of power for the first main secondary endpoint, a sample size of 800 patients, split evenly, ensured that with a 0.025 one-sided significance level test there was more than 80% power to detect a treatment difference of 12.5% versus 20% (odds ratio of 0.571) between HOE901-U300 and Lantus in the incidence of patients with at least one nocturnal hypoglycemia, indicated as severe and/or confirmed by plasma glucose 70 mg/dL that occurred between 00:00 and 05:59, from start of week 9 to endpoint.

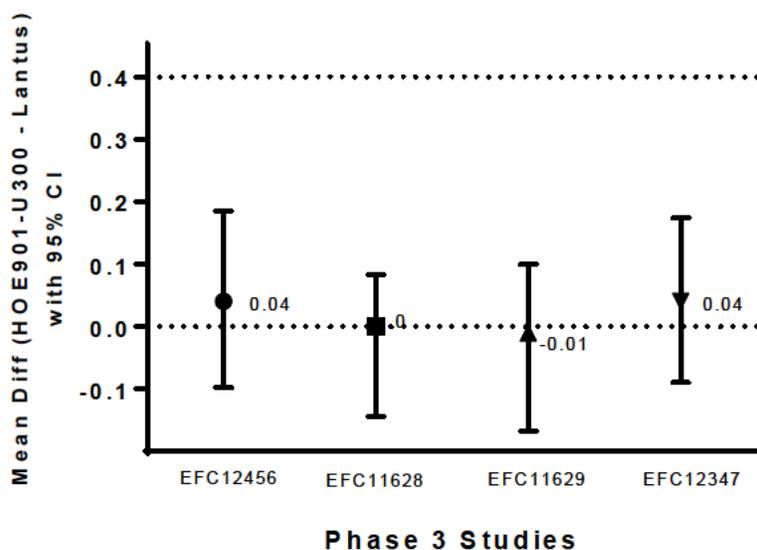
## **6 Review of Efficacy**

### **Efficacy Summary**

The population studied in each trial adequately represented the overall United States population with the few exceptions of the under-representation of Black patients and the exclusion of patients with HbA1c < 7.0% or > 10% ( $\geq 11\%$  in EFC12347).

The Sponsor demonstrated that HOE901-U300 is non-inferior to Lantus in all four pivotal trials (upper bound of the two-sided 95% CI, of difference between HOE901-U300 and Lantus was < 0.4%). See Figure 8 and Table 11 for treatment differences and summary statistics of HbA1c results of pivotal trials. In all 6-month trials, HOE901-U300 reached similar glycemic control, with use of larger total insulin doses (~8-9 units more than Lantus, see Table 12) and greater dose titration of HOE901-U300 compared to Lantus. The increase in dose translates to a 7.7% to 14.8% increase of total insulin dose (U/kg) in the HOE901-U300 group vs. the Lantus group. There was no clear difference in the number of patients requiring rescue therapy (in EFC11629 and EFC12347). However, there was an early rise in SMPG values (pre-breakfast and 8-point measurements) in the HOE901-U300 group for 3 of the 4 studies (except for EFC12347). These slightly higher levels of SMPG measures persisted as pre-breakfast values throughout the main 6-month treatment period for all trials.

**Figure 8 – HbA1c reductions (mITT population) – treatment difference in LS Mean change from baseline**



Note: Treatment difference above 0 favors the comparator (Lantus)

Source: Reviewer graphed data obtained from: all study CSRs section 10.1.1 Primary analysis on primary efficacy endpoint

**Table 11 – Summary statistics for HbA1c results across pivotal trials**

Study (stats analysis)	Treatment group	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change from baseline	
					Raw Mean (SD)	LS Mean (SE)
Type 1 Diabetes						
EFC12456 (MMRM)	HOE901-U300	273	8.13 (0.77)	7.7 (0.99)	-0.42 (0.98)	-0.40 (0.051)
	Lantus	273	8.12 (0.79)	7.68 (0.80)	-0.44 (0.72)	-0.44 (0.051)
Type 2 Diabetes						
EFC11628 (LOCF)	HOE901-U300	404	8.14 (0.78)	7.25 (0.85)	-0.88 (0.81)	-0.83 (0.060)
	Lantus	400	8.14 (0.76)	7.28 (0.92)	-0.86 (0.92)	-0.83 (0.061)
EFC11629 (LOCF)	HOE901-U300	403	8.28 (0.87)	7.57 (1.02)	-0.71 (1.05)	-0.57 (0.094)
	Lantus	405	8.22 (0.77)	7.56 (1.04)	-0.66 (0.90)	-0.56 (0.093)
EFC12347 (MMRM)	HOE901-U300	432	8.49 (1.04)	7.08 (0.96)	-1.40 (1.10)	-1.42 (0.047)
	Lantus	430	8.58 (1.07)	7.05 (0.95)	-1.53 (1.19)	-1.46 (0.048)

Source: all study CSRs section 10.1.1 Primary analysis on primary efficacy endpoint

**Table 12 – Difference in insulin doses (mean U and mean U/kg) between baseline and month 6 across 4 pivotal trials**

Mean basal insulin dose (U)	EFC12456 N=499	EFC11628 N=804	EFC11629 N=808	EFC12347 N=796
<b>Starting dose</b>				
HOE901-U300 -Mean U (Mean U/kg)	27.5 (0.32)	70.3 (0.67)	62.1 (0.64)	18.3 (0.19)
Lantus - Mean U (Mean U/kg)	26.9 (0.32)	70.9 (0.67)	63.9 (0.66)	18.6 (0.19)
Prandial insulin in HOE901-U300 randomized group – Mean U (Mean U/kg)	26.4 (0.32)	54.3 (0.51)		
Prandial insulin in Lantus randomized group- Mean U (Mean U/kg)	25 (0.31)	55.8 (0.51)		
Total daily insulin HOE 901-U300 - Mean U (Mean U/kg)	54 (0.64)	125 (1.19)		
Total daily insulin Lantus - Mean U (Mean U/kg)	51.1 (0.64)	126.5 (1.19)		
<b>Dose at Month 6</b>				
HOE901-U300 - Mean U (Mean U/kg)	40.5 (0.47)	103.3 (0.97)	91 (0.92)	59.4 (0.62)
Lantus - Mean U (Mean U/kg)	34.1 (0.40)	93.7 (0.88)	81.9 (0.84)	52 (0.53)
Unit difference in Mean U <b>basal</b> insulin, (Mean difference in U/kg)*	6.4 (0.07)	9.6 (0.09)	9.1 (0.08)	7.4 (0.09)
<b>% difference in basal insulin (U/kg )<sup>a</sup></b>	<b>+17.5%</b>	<b>+11.4%</b>	<b>+11.9%</b>	<b>+14.8%</b>
Prandial insulin in HOE901-U300 randomized group - Mean U (Mean U/kg)	28.7 (0.34)	59.1 (0.55)		
Prandial insulin in Lantus randomized group - Mean U (Mean U/kg)	27.1 (0.33)	60.5 (0.55)		
Unit difference in Mean U <b>prandial</b> insulin, (Mean difference in U/kg) <sup>^</sup>	1.6 (0.01)	-1.4 (0)		
Total daily insulin in HOE 901-U300 randomized group - Mean U (Mean U/kg)	69.6 (0.81)	163 (1.53)		
Total daily insulin in Lantus randomized group - Mean U (Mean U/kg)	60.9 (0.73)	154.2 (1.43)		
Unit difference in <b>total daily</b> insulin - Mean U (Mean difference in U/kg)**	8.7 (0.08)	8.8 (0.1)	9.1 (0.08)	7.4 (0.09)
<b>% difference in total daily insulin (U/kg)<sup>ab</sup></b>	<b>+11%</b>	<b>+7.7 %</b>	<b>+11.9%</b>	<b>+14.8%</b>
<sup>a</sup> From SCE Table 33 <sup>b</sup> From SCE Table 34 *Unit difference in mean basal insulin = mean <b>basal</b> dose HOE901-U300 – mean <b>basal</b> dose Lantus <sup>^</sup> Unit difference in mean prandial insulin = mean <b>prandial</b> insulin HOE901-U300- mean <b>prandial</b> insulin Lantus ** Unit difference in mean total insulin = mean <b>total</b> insulin HOE901-U300-mean <b>total</b> insulin Lantus % difference in basal insulin = [(HOE901-U300-Lantus)/Lantus] x 100%				
Source: Reviewer obtained the Starting and Month 6 doses (U and U/kg) for basal, prandial and total insulin from individual study CSRs, section 10.2.2.5 (for studies EFC11628, EFC11629, EFC12347), section 10.2.9 for study EFC12456				

(b) (4)

## 6.1 Indication

The sponsor is seeking approval for HOE901-U300 for the treatment of glycemic control in adults with diabetes mellitus, ( i.e. both T1DM and T2DM).

### **6.1.1 Methods**

Details of the methods of individual trials designs are discussed in section 5.2 Review Strategy. In this section, the reviewer evaluates each trial individually in regards to demographics, patient disposition, and efficacy endpoints. Emphasis is placed on factors that may influence the results of these non-inferiority trials.

### **6.1.2 Demographics**

#### EFC12456 - T1DM

When grouping patients by drug treatment, 90% of all participants were <65 years old with a mean age of 47 years. Over half of the participants were male and >85% participants were Caucasian/White. The majority (64%) of those enrolled were living in North America.

The mean BMI $\pm$ SD was 27.6 $\pm$ 5.1 kg/m<sup>2</sup> with a range of 17-51 kg/m<sup>2</sup>. Mean duration of T1DM was 21 years. Half of participants had at least one diabetes complication. Less than 12% of patients had GFR between 30-60 mL/min/1.73m<sup>2</sup>.

The majority of patients randomized to either HOE901-U300 or Lantus were previously on insulin glargine (>60%), prior to starting the study.

**Table 13 - EFC12456 - Subject demographics and baseline characteristics**

	HOE901-U300 Overall (N=274)	Lantus Overall (N=275)	All (N=549)
<b>Age (years)</b>			
Number	274	275	549
Mean (SD)	46.4 (13.9)	48.2 (13.4)	47.3 (13.7)
Median	47.0	49.0	48.0
Min : Max	19 : 80	18 : 86	18 : 86
<b>Age Group (years) [n(%)]</b>			
Number	274	275	549
<65	245 (89.4%)	249 (90.5%)	494 (90.0%)
[65-75[	23 (8.4%)	20 (7.3%)	43 (7.8%)
≥75	6 (2.2%)	6 (2.2%)	12 (2.2%)
<b>Gender [n (%)]</b>			
Number	274	275	549
Male	149 (54.4%)	164 (59.6%)	313 (57.0%)
Female	125 (45.6%)	111 (40.4%)	236 (43.0%)
<b>Race [n (%)]</b>			
Number	274	275	549
Caucasian/White	232 (84.7%)	235 (85.5%)	467 (85.1%)
Black	14 (5.1%)	12 (4.4%)	26 (4.7%)
Asian/Oriental	24 (8.8%)	23 (8.4%)	47 (8.6%)
Other	4 (1.5%)	5 (1.8%)	9 (1.6%)
<b>Ethnicity [n (%)]</b>			
Number	274	275	549
Hispanic	14 (5.1%)	12 (4.4%)	26 (4.7%)
Not Hispanic	260 (94.9%)	263 (95.6%)	523 (95.3%)
<b>World region [n (%)]</b>			
Number	274	275	549
North America	184 (67.2%)	168 (61.1%)	352 (64.1%)
Western Europe	28 (10.2%)	38 (13.8%)	66 (12.0%)
Eastern Europe	38 (13.9%)	47 (17.1%)	85 (15.5%)
Rest of the world	24 (8.8%)	22 (8.0%)	46 (8.4%)
<b>Baseline weight (kg)</b>			
Number	274	275	549
Mean (SD)	81.9 (20.4)	81.8 (16.8)	81.8 (18.7)
Median	79.0	79.0	79.0
Min : Max	44 : 147	43 : 134	43 : 147

	<b>HOE901-U300</b>	<b>Lantus</b>	<b>All</b>
	<b>Overall</b>	<b>Overall</b>	<b>All</b>
	<b>(N=274)</b>	<b>(N=275)</b>	<b>(N=549)</b>
<b>Baseline BMI (kg/m<sup>2</sup>)</b>			
Number	274	275	549
Mean (SD)	27.6 (5.5)	27.6 (4.7)	27.6 (5.1)
Median	27.0	27.0	27.0
Min : Max	17 : 51	19 : 48	17 : 51
<b>Baseline BMI categories (kg/m<sup>2</sup>) [n(%)]</b>			
Number	274	275	549
<25	91 (33.2%)	96 (34.9%)	187 (34.1%)
[25-30[	103 (37.6%)	106 (38.5%)	209 (38.1%)
[30-40[	71 (25.9%)	66 (24.0%)	137 (25.0%)
≥40	9 (3.3%)	7 (2.5%)	16 (2.9%)
<b>Baseline estimated GFR (mL/min/1.73m<sup>2</sup>)</b>			
Number	274	275	549
Mean (SD)	82.71 (19.64)	81.89 (19.49)	82.29 (19.55)
Median	81.97	81.94	81.94
Min : Max	25.3 : 150.8	25.1 : 145.9	25.1 : 150.8
<b>Baseline estimated GFR categories (mL/min/1.73m<sup>2</sup>) [n(%)]</b>			
Number	274	275	549
≥90	97 (35.4%)	80 (29.1%)	177 (32.2%)
[60-90[	144 (52.6%)	161 (58.5%)	305 (55.6%)
[30-60[	31 (11.3%)	32 (11.6%)	63 (11.5%)
<30	2 (0.7%)	2 (0.7%)	4 (0.7%)
<b>Randomization strata of screening HbA1c (%) [n(%)]</b>			
Number	274	275	549
<8	105 (38.3%)	105 (38.2%)	210 (38.3%)
≥8	169 (61.7%)	170 (61.8%)	339 (61.7%)
<b>Randomization strata of geographical region (%) [n(%)]</b>			
Number	274	275	549
Japan	24 (8.8%)	22 (8.0%)	46 (8.4%)
Non-Japan	250 (91.2%)	253 (92.0%)	503 (91.6%)
<b>Patients with at least 1 DM complication [n(%)]</b>			
DM nephropathy	136 (49.6)	143 (52)	279 (50.8)
DM retinopathy	30 (10.9)	27 (9.8)	57 (10.4)
DM retinopathy	102 (37.2)	112 (40.7)	214 (39)
DM sensory or motor neuropathy	66 (24.1)	69 (25.1)	135 (24.6)
DM autonomic neuropathy	7 (2.6)	10 (3.6)	17 (3.1)
DM macroangiopathy	13 (4.7)	8 (2.9)	21 (3.8)

	HOE901-U300 Overall (N=274)	Lantus Overall (N=275)	All (N=549)
<b>Previous insulin glargine daily injection number<sup>a</sup> [n(%)]</b>			
Number	184	168	352
Once daily	159 (86.4%)	149 (88.7%)	308 (87.5%)
Twice daily	25 (13.6%)	19 (11.3%)	44 (12.5%)
More than twice daily	0	0	0
<b>Previous insulin detemir daily injection number<sup>a</sup> [n(%)]</b>			
Number	28	43	71
Once daily	20 (71.4%)	27 (62.8%)	47 (66.2%)
Twice daily	8 (28.6%)	16 (37.2%)	24 (33.8%)
More than twice daily	0	0	0
<b>Previous NPH daily injection number<sup>a</sup> [n(%)]</b>			
Number	6	9	15
Once daily	6 (100%)	5 (55.6%)	11 (73.3%)
Twice daily	0	4 (44.4%)	4 (26.7%)
More than twice daily	0	0	0
<b>Previous basal insulin daily dose<sup>b</sup> (U)</b>			
Number	201	210	411
Mean (SD)	32.27 (20.83)	30.66 (15.30)	31.44 (18.21)
Median	28.00	28.00	28.00
Q1 : Q3	18.00 : 42.00	20.00 : 40.00	19.00 : 40.00
Min : Max	6.0 : 183.0	5.0 : 101.0	5.0 : 183.0
<b>Previous basal insulin daily dose<sup>b</sup> (U/kg)</b>			
Number	201	210	411
Mean (SD)	0.381 (0.173)	0.372 (0.152)	0.376 (0.162)
Median	0.362	0.339	0.351
Q1 : Q3	0.260 : 0.475	0.257 : 0.458	0.260 : 0.461
Min : Max	0.11 : 1.28	0.06 : 0.96	0.06 : 1.28
<b>Previous mealtime insulin analogue type<sup>a</sup> [n(%)]</b>			
Number	258	255	513
Insulin aspart	118 (45.7%)	143 (56.1%)	261 (50.9%)
Insulin lispro	113 (43.8%)	90 (35.3%)	203 (39.6%)
Insulin glulisine	28 (10.9%)	23 (9.0%)	51 (9.9%)

Source: Adapted from Study CSR Table 10, Table 11 and Appendix 16.2.4 EFC12456: Demographic data, data at baseline and medication details

**Reviewer's comment: The population reasonably represents the general population with Type 1 diabetes. Baseline characteristics were balanced suggesting that the effect of randomization was preserved. However, non-White patients are underrepresented.**

**It is important to note that the majority of patients (>60%) were taking Lantus prior to randomization. Lantus was the open-label comparator in this trial. It is possible that the familiarity with this insulin may have biased participants to over/under report subjective events if randomized to the Lantus intervention arm.**

**EFC11628 - T2DM**

Overall, patients were equally randomized to either study drug. Over half of patients were male, younger than 65 years of age, from North America, had an HbA<sub>1c</sub> ≥ 8%, and were obese with a BMI between 30-40 kg/m<sup>2</sup>. A large proportion of patients were Caucasian/White (over 90% in both groups). A third of patients were 65 years old or older, with <5% being over the age of 75 years of age. More than 90% of patients in each treatment group were previously on Lantus prior to randomization.

**Table 14 - EFC11628 - Subject demographics and baseline characteristics**

	HOE901-U300 (N=404)	Lantus (N=403)	All (N=807)
<b>Age (years)</b>			
Number	404	403	807
Mean (SD)	60.1 (8.5)	59.8 (8.7)	60.0 (8.6)
Median	61.0	60.0	61.0
Min : Max	28 : 83	32 : 86	28 : 86
<b>Age Group (years) [n(%)]</b>			
Number	404	403	807
<65	277 (68.6%)	284 (70.5%)	561 (69.5%)
[65-75[	114 (28.2%)	105 (26.1%)	219 (27.1%)
≥75	13 (3.2%)	14 (3.5%)	27 (3.3%)
<b>Gender [n (%)]</b>			
Number	404	403	807
Male	217 (53.7%)	210 (52.1%)	427 (52.9%)
Female	187 (46.3%)	193 (47.9%)	380 (47.1%)
<b>Race [n (%)]</b>			
Number	404	403	807
Caucasian/White	371 (91.8%)	374 (92.8%)	745 (92.3%)
Black	26 (6.4%)	21 (5.2%)	47 (5.8%)
Asian/Oriental	6 (1.5%)	5 (1.2%)	11 (1.4%)
Other	1 (0.2%)	3 (0.7%)	4 (0.5%)

	<b>HOE901-U300</b> (N=404)	<b>Lantus</b> (N=403)	<b>All</b> (N=807)
<b>Ethnicity [n (%)]</b>			
Number	404	403	807
Hispanic	26 (6.4%)	25 (6.2%)	51 (6.3%)
Not Hispanic	378 (93.6%)	378 (93.8%)	756 (93.7%)
<b>World region [n (%)]</b>			
Number	404	403	807
North America	206 (51.0%)	207 (51.4%)	413 (51.2%)
Western Europe	33 (8.2%)	33 (8.2%)	66 (8.2%)
Eastern Europe	147 (36.4%)	141 (35.0%)	288 (35.7%)
Rest of the world	18 (4.5%)	22 (5.5%)	40 (5.0%)
<b>Baseline weight (kg)</b>			
Number	404	403	807
Mean (SD)	106.2 (21.5)	106.4 (20.0)	106.3 (20.8)
Median	104.3	104.1	104.1
Min : Max	60 : 197	62 : 164	60 : 197
<b>Baseline BMI (kg/m<sup>2</sup>)</b>			
Number	404	403	807
Mean (SD)	36.6 (6.8)	36.6 (6.1)	36.6 (6.4)
Median	35.8	36.0	35.9
Min : Max	23 : 62	24 : 62	23 : 62
<b>Baseline BMI categories (kg/m<sup>2</sup>) [n(%)]</b>			
Number	404	403	807
<25	5 (1.2%)	2 (0.5%)	7 (0.9%)
[25-30[	54 (13.4%)	47 (11.7%)	101 (12.5%)
[30-40[	241 (59.7%)	244 (60.5%)	485 (60.1%)
≥40	104 (25.7%)	110 (27.3%)	214 (26.5%)
<b>Baseline estimated GFR (mL/min/1.73m<sup>2</sup>)</b>			
Number	404	403	807
Mean (SD)	73.68 (19.33)	74.78 (21.38)	74.23 (20.37)
Median	73.62	75.69	74.41
Min : Max	19.9 : 144.2	15.0 : 141.5	15.0 : 144.2
<b>Baseline estimated GFR categories (mL/min/1.73m<sup>2</sup>) [n(%)]</b>			
Number	404	403	807
≥90	75 (18.6%)	89 (22.1%)	164 (20.3%)
[60-90[	234 (57.9%)	221 (54.8%)	455 (56.4%)
[30-60[	93 (23.0%)	83 (20.6%)	176 (21.8%)
<30	2 (0.5%)	10 (2.5%)	12 (1.5%)

	<b>HOE901-U300 (N=404)</b>	<b>Lantus (N=403)</b>	<b>All (N=807)</b>
<b>Duration of T2D (years)</b>			
Number	404	403	807
Mean (SD)	15.6 (7.2)	16.1 (7.8)	15.8 (7.5)
Median	15.2	15.2	15.2
Min : Max	2 : 43	2 : 44	2 : 44
<b>Category of duration of T2D (years)</b>			
Number	404	403	807
<10	90 (22.3%)	84 (20.8%)	174 (21.6%)
≥10	314 (77.7%)	319 (79.2%)	633 (78.4%)
<b>Age at onset of T2D (years)</b>			
Number	404	403	807
Mean (SD)	45.0 (8.8)	44.2 (9.5)	44.6 (9.2)
Median	44.9	44.4	44.7
Min : Max	18 : 78	15 : 73	15 : 78
<b>Duration of basal insulin treatment (years)</b>			
Number	404	403	807
Mean (SD)	6.71 (4.74)	6.48 (4.78)	6.59 (4.76)
Median	5.50	5.20	5.40
Min : Max	0.3 : 32.8	1.0 : 33.2	0.3 : 33.2
<b>Previous basal insulin type<sup>a</sup> [n(%)]</b>			
Number	402	399	801
Insulin glargine	372 (92.5%)	365 (91.5%)	737 (92.0%)
NPH	30 (7.5%)	34 (8.5%)	64 (8.0%)
<b>Randomization strata of screening HbA1c (%) [n(%)]</b>			
Number	404	403	807
<8	144 (35.6%)	144 (35.7%)	288 (35.7%)
>8	260 (64.4%)	259 (64.3%)	519 (64.3%)
<b>Patients with DM complication [n(%)]</b>			
DM nephropathy	92 (22.8%)	93 (23.1%)	185 (22.9%)
DM retinopathy	121 (30 %)	141 (35%)	262 (32.5%)
DM sensory or motor neuropathy	158 (39.1%)	170 (42.2%)	328 (40.6%)
DM autonomic neuropathy	16 (4%)	14 (3.5%)	30 (3.7%)
DM macroangiopathy	42 (10.4%)	47 (11.7%)	89 (11%)

Source: Adapted from Study CSR Table 10, Appendix 16.2.4

<sup>a</sup> Previous basal insulin type and maximal injection number of patient during the last 7 days prior to randomization

At baseline, treatment groups were balanced regarding concomitant medical disorders (data not shown) with the most commonly reported being vascular disorders in over 80% of patients.

**Reviewer's comment: As with the T1DM study (EFC12456), most of the patients in this study were previously on Lantus prior to randomization.**

**Overall, the patient demographics suggest appropriate randomization.**

#### EFC11629 – T2DM

The demographic and baseline characteristics were similar between the 2 treatment groups (See Table 15). Over a fifth of patients were  $\geq 65$  years with more than half of all patients being female. The majority of patients were Caucasian ( $>90\%$ ). More than a quarter of patients were obese with slightly higher numbers in the HOE901-U300 group. Overall, treatment arms were well balanced regarding underlying or prior disorders, with the most frequently reported disease being vascular disorder (81.6% of patients).

**Table 15 – EFC11629 – Subject demographics and baseline characteristics**

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
<b>Age (years)</b>			
Number	404	407	811
Mean (SD)	57.9 (9.1)	58.5 (9.2)	58.2 (9.2)
Median	59.0	59.0	59.0
Min : Max	24 : 84	27 : 80	24 : 84
<b>Age Group (years) [n(%)]</b>			
Number	404	407	811
<65	317 (78.5%)	304 (74.7%)	621 (76.6%)
[65-75[	80 (19.8%)	88 (21.6%)	168 (20.7%)
≥75	7 (1.7%)	15 (3.7%)	22 (2.7%)
<b>Gender [n (%)]</b>			
Number	404	407	811
Male	187 (46.3%)	185 (45.5%)	372 (45.9%)
Female	217 (53.7%)	222 (54.5%)	439 (54.1%)
<b>Race [n (%)]</b>			
Number	404	407	811
Caucasian/White	378 (93.6%)	383 (94.1%)	761 (93.8%)
Black	20 (5.0%)	16 (3.9%)	36 (4.4%)
Asian/Oriental	3 (0.7%)	7 (1.7%)	10 (1.2%)
Other	3 (0.7%)	1 (0.2%)	4 (0.5%)
<b>Ethnicity [n (%)]</b>			
Number	404	407	811
Hispanic	102 (25.2%)	91 (22.4%)	193 (23.8%)
Not Hispanic	302 (74.8%)	316 (77.6%)	618 (76.2%)
<b>World region [n (%)]</b>			
Number	404	407	811
North America	175 (43.3%)	194 (47.7%)	369 (45.5%)
Western Europe	40 (9.9%)	43 (10.6%)	83 (10.2%)
Eastern Europe	122 (30.2%)	103 (25.3%)	225 (27.7%)
Rest of the world	67 (16.6%)	67 (16.5%)	134 (16.5%)
<b>Baseline weight (kg)</b>			
Number	404	407	811
Mean (SD)	98.7 (22.3)	98.0 (20.8)	98.3 (21.6)
Median	94.4	95.0	95.0
Min : Max	48 : 209	48 : 188	48 : 209

	HOE901-U300 (N=404)	Lantus (N=407)	All (N=811)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>			
Number	404	407	811
Mean (SD)	34.8 (6.6)	34.8 (6.1)	34.8 (6.4)
Median	33.6	34.0	33.8
Min : Max	20 : 63	21 : 59	20 : 63
<b>Baseline BMI categories (kg/m<sup>2</sup>) [n(%)]</b>			
Number	404	407	811
<25	11 (2.7%)	5 (1.2%)	16 (2.0%)
[25-30[	91 (22.5%)	90 (22.1%)	181 (22.3%)
[30-40[	215 (53.2%)	244 (60.0%)	459 (56.6%)
≥40	87 (21.5%)	68 (16.7%)	155 (19.1%)
<b>Baseline estimated GFR (mL/min/1.73m<sup>2</sup>)</b>			
Number	404	407	811
Mean (SD)	82.01 (21.73)	80.47 (20.89)	81.23 (21.31)
Median	81.11	78.69	79.84
Min : Max	22.7 : 155.3	25.1 : 158.8	22.7 : 158.8
<b>Baseline estimated GFR categories (mL/min/1.73m<sup>2</sup>) [n(%)]</b>			
Number	404	407	811
≥90	134 (33.2%)	132 (32.4%)	266 (32.8%)
[60-90[	213 (52.7%)	218 (53.6%)	431 (53.1%)
[30-60[	55 (13.6%)	55 (13.5%)	110 (13.6%)
<30	2 (0.5%)	2 (0.5%)	4 (0.5%)
<b>Randomization strata of screening HbA1c (%) [n(%)]</b>			
Number	404	407	811
<8	144 (35.6%)	146 (35.9%)	290 (35.8%)
≥8	260 (64.4%)	261 (64.1%)	521 (64.2%)
<b>Patients with DM complication [n(%)]</b>			
Diabetic nephropathy	66 (16.4%)	54 (13.3%)	120 (14.8%)
Diabetic retinopathy	108 (26.8%)	85 (20.9%)	193 (23.8%)
Diabetic sensory or motor neuropathy	157 (39.0%)	144 (35.4%)	301 (37.2%)
Diabetic autonomic neuropathy	5 (1.2%)	6 (1.5%)	11 (1.4%)
Diabetic macroangiopathy	33 (8.2%)	26 (6.4%)	59 (7.3%)

Table adapted from Study CSR Table 10 and EFC 11629, Demographic data 16.2.4.

Prior to the study most patients were receiving insulin or insulin analogs for injection (99.8%), with the majority using glargine (79.0%) and the remainder NPH. Biguanides (e.g. metformin) were used by the majority of participants (>90%). Concomitant medication used 3 months prior to study up to the first injection of IMP was similar to those used during the 6-month treatment period. Overall, there were greater number of patients in the Lantus group taking

thiazolidinediones and combinations of oral blood glucose lowering drugs compared to the HOE901-U300 group. However, the HOE901-U300 group had greater numbers of patients taking insulins and analogues injection that were intermediate acting (see Table 16).

**Table 16 – EFC11629 - Antidiabetic medications taken by the patients in the 3 months before screening up to the first injection of IMP**

	<b>HOE901-U300 (N=404)</b>	<b>Lantus (N=407)</b>
any blood glucose lowering drugs	403 (99.8%)	406 (99.8%)
blood glucose lowering drugs excl. insulins	403 (99.8%)	406 (99.8%)
Biguanides	388 (96%)	383 (94.1%)
Dipeptidyl peptidase 4 (dpp-4) inhibitors	33 (8.2%)	51 (12.5%)
Other blood glucose lowering drugs, excl. insulins	11 (2.7%)	18 (4.4%)
Sulfonamides, urea derivatives	18 (4.5%)	12 (2.9%)
Thiazolidinediones	6 (1.5%)	16 (3.9%)
Combinations of oral blood glucose lowering drugs	6 (1.5%)	11(2.7%)
Alpha glucosidase inhibitors	4 (1%)	1 (0.2%)
Insulins and analogues	403 (99.8%)	406 (99.8%)
Insulins and analogues for injection, long acting	304 (75.2%)	338 (83%)
Insulin glargine	304 (75.2%)	337 (82.8%)
Insulin detemir	1 (0.2%)	3 (0.7%)
Insulin degludec	0	1 (0.2%)
Insulins and analogues injection, intermediate acting	103 (25.5%)	75 (18.4%)
Insulin and analogues for injection, intermediate-acting combined with fast acting	5 (1.2%)	5 (1.2%)
Insulins and analogues for injection, fast acting	0	3 (0.7%)

Source: adapted from study CSR demo-data, Table 4

Overall, the distribution of antidiabetic medications (see above) taken by patients were mostly balanced and suggest appropriate randomization.

#### EFC12347 - T2DM

The demographic and baseline characteristics were similar in the two treatment groups. Over 50% of the randomized participants were male, and 78% of patients were Caucasian. The majority (>70%) of patients were less than 65 years of age with most (>50%) having duration of diabetes of less than 10 years (see Table 17). All patients received non-insulin antihyperglycemic therapy in the 3 months prior to randomization. The duration of prior non-insulin therapy ranged from less than a year to over 25 years and was similar between the two groups.

**Table 17 - EFC12347 - Subject demographics and baseline characteristics**

	<b>HOE901-U300 (N=439)</b>	<b>Lantus (N=439)</b>	<b>Total (N=478)</b>
<b>Age (yrs.)</b>			
Number	439	439	878
Mean(SD)	58.2 (9.9)	57.2 (10.3)	57.7 (10.1)
<65 [n (%)]	324 (73.8%)	328 (74.7%)	652 (74.3%)
65-75 [n (%)]	98 (22.3%)	92 (21.0%)	190 (21.6%)
≥75 [n (%)]	17 (3.9%)	19 (4.3%)	36 (4.1%)
<b>Gender [n (%)]</b>			
Male	253 (57.6%)	254 (57.9%)	507 (57.7%)
<b>Race [n (%)]</b>			
Caucasian/White	347 (79.0%)	338 (77.0%)	685 (78.0%)
Black	44 (10.0%)	57 (13.0%)	101 (11.5%)
Asian/Oriental	39 (8.9%)	37 (8.4%)	76 (8.7%)
Other	9 (2.1%)	7 (1.6%)	16 (1.8%)
<b>World region [n (%)]</b>			
North America	319 (72.7%)	319 (72.7%)	638 (72.7%)
Western Europe	27 (6.2%)	30 (6.8%)	57 (6.5%)
Eastern Europe	68 (15.5%)	65 (14.8%)	133 (15.1%)
Rest of the world	25 (5.7%)	25(5.7%)	50 (5.7%)
<b>Baseline weight (kg)</b>			
Mean(SD)	95.1 (23.3)	95.6 (22.6)	95.3 (22.9)
Min : Max	43 : 173	48 : 190	43 : 190
<b>Baseline BMI (kg/m<sup>2</sup>)</b>			
Mean(SD)	32.8 (6.9)	33.2 (6.6)	33.0 (6.7)
Min : Max	18 : 55	20 : 55	18 : 55
<25 [n (%)]	48 (10.9%)	40 (9.1%)	88 (10.0%)
25-30 [n (%)]	121 (27.6%)	110 (25.1%)	231 (26.3%)
30-40 [n (%)]	198 (45.1%)	222 (50.6%)	420 (47.8%)
≥40 [n (%)]	72 (16.4%)	67 (15.3%)	139 (15.8%)
<b>Baseline estimated GFR (mL/min/1.73m<sup>2</sup>)</b>			
Mean(SD)	81.32 (19.57)	80.72 (19.87)	81.02 (19.71)
Min : Max	25.9 : 137.1	28.5 : 172.2	25.9 : 172.2
≥90 [n (%)]	127 (28.9%)	128 (29.2%)	255 (29.0%)
60-90 [n (%)]	256 (58.3%)	248 (56.5%)	504 (57.4%)
30-60 [n (%)]	53 (12.1%)	62 (14.1%)	115 (13.1%)
<30 [n (%)]	3 (0.7%)	1 (0.2%)	4 (0.5%)
<b>Randomization strata of geographical region [n(%)]</b>			
Japan	25 (5.7%)	25 (5.7%)	50 (5.7%)
Non-Japan	414 (94.3%)	414 (94.3%)	828 (94.3%)
<b>Randomization strata of screening HbA1c (%) [n(%)]</b>			
<8	141 (32.1%)	142 (32.3%)	283 (32.2%)
≥8	298 (67.9%)	297 (67.7%)	595 (67.8%)

Source study CSR Table 9

**Reviewer’s comment: Overall baseline and demographic characteristics were similar between the HOE901-U300 and Lantus groups and were adequately reflective of patients with T2DM.**

Over 90% of patients took biguanides within 3 months before randomization and over 50% took sulfonylureas. The distribution of the non-insulin therapies was similar between the two treatment groups (see Table 18).

**Table 18 - EFC12347 - Summary of disease characteristics at baseline - randomized population**

	HOE901-U300 (N=439)	Lantus (N=439)	All (N=878)
<b>Duration of T2D (years)</b>			
Number	435	436	871
Mean (SD)	10.11 (6.49)	9.57 (6.22)	9.84 (6.36)
Min : Max	1.0 : 46.1	0.4 : 35.1	0.4 : 46.1
<b>Category of duration of T2D (years)</b>			
Number	435	436	871
<10	241 (55.4%)	258 (59.2%)	499 (57.3%)
≥10	194 (44.6%)	178 (40.8%)	372 (42.7%)
<b>Age at onset of T2D (years)</b>			
Mean (SD)	48.5 (9.9)	48.2 (10.0)	48.4 (10.0)
Min : Max	16 : 72	19 : 77	16 : 77
<b>At least one diabetic complication</b>			
Diabetic nephropathy	34 (7.7%)	23 (5.2%)	57 (6.5%)
Diabetic retinopathy	62 (14.1%)	52 (11.8%)	114 (13.0%)
Diabetic sensory or motor neuropathy	117 (26.7%)	97 (22.1%)	214 (24.4%)
Diabetic autonomic neuropathy	9 (2.1%)	9 (2.1%)	18 (2.1%)
Diabetic macroangiopathy	11(2.5%)	5 (1.1%)	16 (1.8%)
<b>Duration of prior non-insulin antihyperglycemic treatment (years)</b>			
Mean (SD)	4.03 (4.50)	4.13 (4.29)	4.08 (4.39)
Min : Max	0.003 : 25.952	0.030 : 32.969	0.003 : 32.969
<b>Prior non-insulin antihyperglycemic treatment<sup>a</sup></b>			
Number	435	437	872
Biguanides	394 (90.6%)	402 (92.0%)	796 (91.3%)
Sulfonamides, urea derivatives	257 (59.1%)	256 (58.6%)	513 (58.8%)
Dipeptidyl peptidase 4 (dpp-4) inhibitors	90 (20.7%)	98 (22.4%)	188 (21.6%)
Other blood glucose lowering drugs, excl. insulins	31 (7.1%)	28 (6.4%)	59 (6.8%)
Thiazolidinediones	25 (5.7%)	29 (6.6%)	54 (6.2%)
Combinations of oral blood glucose lowering drugs <sup>b</sup>	24 (5.5%)	25 (5.7%)	49 (5.6%)
Alpha glucosidase inhibitors	8 (1.8%)	14 (3.2%)	22 (2.5%)

<sup>a</sup> Taken within 3 months before randomization

<sup>b</sup> Combinations of oral blood glucose lowering drugs are referring to the fixed dose combinations in a single final pharmaceutical form.

Source: study CSR, Table 10 and Table 11

**Reviewer’s comment regarding demographics conclusions: Across all trials, randomization groups were generally well balanced with some small differences that should not affect efficacy analyses.**

### 6.1.3 Subject Disposition

For each study, the patients’ disposition is shown below. This section evaluates the patient’s disposition by considering the impact it may have on the efficacy evaluation. The study quality is also evaluated in light of the study disposition. Discontinuation due to adverse events and discontinuation due other reasons, is discussed for the safety population in section 7.3.3 Dropouts and/or Discontinuations.

As shown in the following sections, the dropout rates observed in each trial are generally reasonable for 6-month trial, and missing data would not be expected to be a significant problem for these trials. However, refer to the Statistical review for a full evaluation of the impact of missing data on the efficacy analyses.

#### EFC12456 – T1DM

A total of 846 patients were screened, of whom 297 patients (35.1%) were screen failures; the most common reason for screening failure was HbA1c <7.0% or >10% at the screening visit (126 patients [14.9%]). Out of the 549 randomized patients, 1 (0.4%) patient in the HOE901-U300 overall group and 2 (0.7%) patients in the Lantus overall group were **excluded** from the mITT efficacy analyses because of missing baseline and post baseline efficacy endpoint data during the main 6-month on-treatment period.

Important deviations of patients that did not exclude them from the mITT population but affected efficacy analyses were:

- No post-baseline HbA1c measurement during the main 6-month on-treatment period -- HOE901-U300: 15 (5.5%) vs. Lantus: 9 patients (3.3%)
- Deviations related to drug dispensing irregularities -- in each treatment group: 10 patients (3.6%).
- Protocol deviations (most due to antidiabetic treatment given during the study other than IMP and mealtime insulin) -- HOE901-U300: 29 (10.6%) vs. Lantus: 34 (12.4%)

Two sites were closed during this study:

- site in the USA closed due to Investigator’s wish to stop participation. The 2 patients that were randomized withdrew from the study.
- site in Hungary was closed due to investigator leaving the site. 3 patients randomized in this site were discontinued from the study.

During the main 6-month on treatment period, the percentage of patients who discontinued treatment was 15.7% in the HOE901-U300 overall group compared with 14.2% in the Lantus overall group. There were no differences in dropout rate based on time of day of injection.

**Table 19 - EFC12456 – Patient disposition - randomized population**

Subjects, n (%)
-----------------

	HOE901-U300			Lantus			All
	AM injection	PM injection	Overall	AM injection	PM injection	Overall	All
Randomized n (%)	136 (100)	138 (100)	<b>274 (100)</b>	137 (100)	138 (100)	<b>275 (100)</b>	549 (100)
Efficacy mITT n (%)	136 (100)	137 (99.3)	<b>273 (99.6)</b>	135 (98.5)	138 (100)	<b>273 (99.3)</b>	546 (99.5)
Month 6 completers n (%)	115 (84.6)	116 (84.1)	<b>231 (84.3)</b>	118 (86.1)	118 (85.5)	<b>236 (85.8)</b>	467 (85.1)
Safety population	135	139	<b>274</b>	136	139	<b>275</b>	549
Randomized and treated n(%)	136 (100)	138 (100)	<b>274 (100)</b>	137 (100)	138 (100)	<b>275 (100)</b>	
Permanently discontinued during 6-month period n(%)	21 (15.4)	22 (15.9)	<b>43 (15.7)</b>	19 (13.9)	20 (14.5)	<b>39 (14.2)</b>	
Reasons for treatment discontinuation n(%)							
Adverse event n(%)	3 (2.2)	0	<b>3 (1.1)</b>	2 (1.5)	2 (1.4)	<b>4 (1.5)</b>	
Lack of efficacy n(%)	2 (1.5)	2 (1.4)	<b>4 (1.5)</b>	1 (0.7)	0	<b>1 (0.4)</b>	
Poor compliance to Protocol n(%)	3 (2.2)	6 (4.3)	<b>9 (3.3)</b>	1 (0.7)	3 (2.2)	<b>4 (1.5)</b>	
Other reasons n(%)	13 (9.6)	13 (9.4)	<b>26 (9.5)</b>	15 (10.9)	15 (10.9)	<b>30 (10.9)</b>	
Missing n(%)	0	1 (0.7)	<b>1 (0.4)</b>	0	0	<b>0</b>	

Source: adapted from Appendix 16.2.1 Patient disposition

#### Reviewer's comment:

**The number of patients excluded due to site closures was small and likely does not have a large impact on the efficacy findings. Other important deviations of patients that did not exclude them from the mITT but affected efficacy (such as no post-baseline HbA1c or drug dispensing irregularities) were balanced between the treatment groups.**

**The patients excluded due to missing baseline and post baseline endpoint were appropriately excluded from the primary efficacy analysis as per the Sponsor's SAP.**

**The percentage of patients who permanently discontinued in this study was close to double the patients in any of the T2DM trials (except trial EFC12347). The reason for this higher discontinuation of the trial is unclear. The extent of missing data is likely to affect the efficacy results more than any other trials.**

#### EFC11628 - T2DM

Of 1,177 patients screened, of whom 370 (31 %) were screen failures. The most common reason for screening failure was HbA1c out of range (HbA1c <7.0% or >10%) from protocol. Of the 807 patients randomized to HOE901-U300 (404 patients) or Lantus (403 patients), 1 patient (in the Lantus group) was **excluded** from the mITT analysis due to lack of treatment despite randomization.

Important deviations of patients that did not exclude them from mITT population but affected efficacy analyses were:

- No post-baseline HbA1c value during the main 6-month on treatment period -- HOE901-U300: 13 (3.2%) vs. Lantus: 6 (1.5%)
- Dosing irregularities -- HOE901-U300: 24 (5.9%) vs. Lantus: 18 (4.5%)

- protocol deviations (most due to patient receiving protocol prohibited medication) --  
HOE901-U300: 32(7.9%) vs. Lantus: 28 (6.9%)

One site closed during this study due to bankruptcy. The 2 patients that were screened and randomized at this site were transferred to another site.

During the main 6-month on-treatment period, the percentage of patients who discontinued treatment was 7.4% in the HOE901-U300 group compared with 7.7% in the Lantus group.

**Table 20 – EFC11628 - Patient disposition - randomized population**

	<b>HOE901- U300 N=404</b>	<b>Lantus N=403</b>
Randomized and treated (%)	404 (100%)	402 (99.8%)
Completed 6-month treatment period n(%)	374 (92.6%)	371 (92.1)
Permanently discontinued during 6-month period n(%)	30 (7.4)	31 (7.7)
Reasons for treatment discontinuation n(%)		
Adverse event n(%)	9 (2.2)	8 (2)
Lack of efficacy n(%)	1 (0.2)	1 (0.2)
Poor compliance to protocol n(%)	2 (0.5)	5 (1.2)
Other reasons n(%)	18 (4.5)	17 (4.2)

Source: modified from Study CSR Table 7

**Reviewer’s comments: The patients excluded from the mITT analysis were appropriate based on the pre-specified study SAP. Other important deviations of patients that did not exclude them from the mITT but affected efficacy (such as no post-baseline HbA1c or drug dispensing irregularities) were higher in the HOE90-U300 group compared to the Lantus group. However, the number of patients excluded, is small and not likely to affect the efficacy findings.**

**The number of patients who discontinued the study was small and was balanced between the two treatment groups. The impact of patient discontinuation on the efficacy findings on this trial is likely small.**

EFC11629 - Type 2 Diabetes

Of 1250 patients that were screened, 439 (35.1%) were screen failures. Most screen failures were due to HbA1c being outside the prespecified HbA1c range (20.8%). Out of the 811 randomized patients, two patients were **excluded** from the mITT analysis (one in each treatment arm), due to lack of receiving study treatment.

Important deviations of patients that did not exclude them from mITT population but affected efficacy analyses were:

- No post-baseline HbA1c value during the main 6-month on –treatment period --HOE901-U300: 16 (4%) vs. Lantus: 13 (3.2%)
- drug dispensing irregularities -- HOE901-U300: 12 (3%) vs. Lantus: 11 (2.7%)
- protocol deviations (most due to patient receiving protocol prohibited medication) -- HOE901-U300: 26 (6.4%) vs. Lantus: 23 (5.7%)

Slightly greater number of patients required rescue therapy (HOE901-U300 5.7% vs. Lantus 4.9%, see Table 21). The efficacy data from these patients reflects values obtained prior to rescue. Close to 9% of patients in each treatment arm permanently discontinued the trial.

**Table 21 - EFC11629 - Patient disposition - randomized population**

	<b>HOE901-U300 N=404</b>	<b>Lantus N=407</b>
Randomized and treated (%)	403 (99.8%)	404 (99.8%)
Completed 6-month treatment period n(%)	344 (85.1%)	349 (85.7%)
Permanently discontinued during 6-month period n(%)	36 (8.9%)	38 (9.3%)
Rescue intake during the main 6-month period	23 (5.7%)	20 (4.9%)
Reasons for treatment discontinuation n(%)		
Adverse event n(%)	6 (1.5%)	4 (1.0%)
Lack of efficacy n(%)	2 (0.5%)	0
Poor compliance to protocol n(%)	4 (1%)	4 (1%)
Other reasons n(%)	24 (5.9%)	30 (7.4%)

Source: modified from Study CSR Table 7

**Reviewer’s comments: The patients excluded from the mITT analysis were appropriate based on the pre-specified study SAP. There was no meaningful difference in the number of patients who required rescue between treatment groups, although there was a greater numerical percentage in the HOE901-U300 arm (5.7%) vs. Lantus (4.9%).**

**Other important deviations of patients that did not exclude them from the mITT but affected efficacy (such as no post-baseline HbA1c or drug dispensing irregularities) were similar between treatment groups and overall small.**

EFC12347 - T2DM

Of 1,396 patients screened, 518 (37.1%) were screen failures. The majority of screening failure was due to HbA1c outside of prespecified range ( $\geq 11\%$  or  $< 7\%$ ). Of the 878 patients that were randomized, 16 patients (7 in HOE901-U300 and 9 in the Lantus group) were **excluded** from the mITT analysis due to the following reasons:

- Randomized but not treated: 4 (0.9%) patients in the HOE901-U300 and 1 (0.2%) in the Lantus group

- No baseline and post baseline efficacy endpoint during the main 6-month on-treatment period: 7(1.6%) in HOE901-U300 vs. 9 (2.1%) in the Lantus group

Important deviations of patients that did not exclude them from mITT population but affected efficacy analyses were:

- No post-baseline HbA1c value during the main 6-month on –treatment period – HOE901-U300: 22 (5%) vs. Lantus: 23 (5.2%)
- drug dispensing irregularities – HOE901-U300: 13 (3%) vs. Lantus: 9 (2.1%)
- protocol deviations (most due to patient receiving protocol prohibited medication) -- HOE901-U300: 36 (8.2%) vs. Lantus: 41 (9.3%)

During the main 6-month on-treatment period the percentage of patients who discontinued treatment was higher in the Lantus group (17.1%) vs. the HOE901-U300 group (14.1%), see Table 22.

Rescue therapy was started in fewer patients in the HOE901-U300 (1.6%) vs Lantus (3.4%) group. Efficacy evaluations of these patients were based on data collected prior to start of rescue medication.

**Table 22 - EFC12347 - Patient disposition - randomized population**

	<b>HOE901-U300 N=439</b>	<b>Lantus N=439</b>
Randomized and treated (%)	435 (99.1)	438 (99.8)
Completed 6-month treatment period n(%)	366 (83.4)	350 (79.7)
Permanently discontinued during 6-month period n(%)	62 (14.1)	57 (17.1)
Rescue intake during the main 6-month period	7 (1.6)	15 (3.4)
Reasons for treatment discontinuation n(%)		
Adverse event n(%)	6 (1.4)	5 (1.1)
Lack of efficacy n(%)	1 (0.2)	4 (0.9)
Poor compliance to protocol n(%)	6 (1.4)	8 (1.8)
Other reasons n(%)	49 (11.2)	59 (13.2)

Source: modified Study CSR, table 5

**Reviewer’s comments:**

**There was a greater number of screened patients that were excluded in this protocol compared to others, despite the larger range of HbA1c for qualification ( $\geq 11\%$  or  $< 7\%$ ). Overall, this T2DM trial, had a greater number of deviations (including those that excluded patients from the mITT population) than other trials. The number of patients who permanently discontinued the study is close to double the number of patients in each of the other T2DM trials (EFC11628 and EFC11629). Both of these factors (deviations and discontinuations), taken together likely affected the efficacy results of this trial. Although these factors may have affected the efficacy results of this study, the overall completer rate**

**is sufficiently high and sensitivity analyses showed that missing data did not affect the primary efficacy analysis, hence suggesting that the effect of these factors was small. The number of deviations, although higher than other studies, was balanced between treatment groups, and less likely to favor one treatment group (e.g. HOE901-U300)**

**Unlike trial EFC11629, there was a greater number of patients who required rescue in the Lantus arm compared to the HOE901-U300 arm.**

#### **6.1.4 Analysis of Primary Endpoint(s)**

For the statistical review, please refer to Anna Kettermann's analysis of the primary endpoint for all studies. The analyses presented below are the Sponsor's analyses, provided in the Complete Study Reports for each respective study.

The analysis presented for the type 1 diabetes trial (EFC 12456) is located in the following sections:

- 6.1.4.1.1 Primary efficacy endpoint - EFC12456 - T1DM
- 6.1.4.1.2 Secondary efficacy endpoints - EFC12456 – T1DM
- 6.1.4.1.3 Other Endpoints - EFC12456 – T1DM
- 6.1.4.1.4 Subpopulations - EFC12456 – T1DM

Similarly, sections for the type 2 diabetes trials are as follow:

EFC11628:

- 6.1.4.2.1 Primary efficacy endpoint - EFC11628 – T2DM patients taking IMP plus meal time insulin
- 6.1.4.2.2 Secondary efficacy endpoints - EFC11628 – T2DM
- 6.1.4.2.3 Other Endpoints - EFC11628 – T2DM
- 6.1.4.2.4 Subpopulations - EFC11628 –T2DM

EFC11629:

- 6.1.4.3.1 Primary efficacy endpoint - EFC11629 - T2DM patients taking oral antihyperglycemic drugs(s)
- 6.1.4.3.2 Secondary endpoints - EFC11629 - T2DM
- 6.1.4.3.3 Other endpoints - EFC11629 - T2DM
- 6.1.4.3.4 Subpopulations - EFC11629- T2DM

EFC12347:

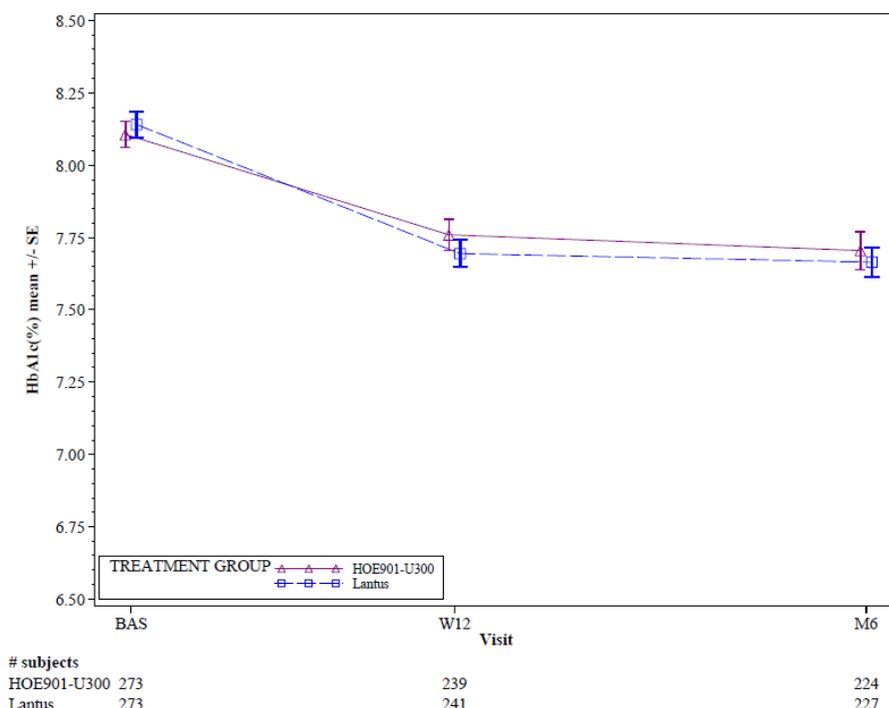
- 6.1.4.4.1 Primary efficacy endpoint - EFC12347 –T2DM insulin naive
- 6.1.4.4.2 Secondary endpoints - EFC12347
- 6.1.4.4.3 Other endpoints - EFC12347
- 6.1.4.4.4 Subpopulations - EFC12347

In section *6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations*, the review again pertains to both trials.

### 6.1.4.1.1 Primary efficacy endpoint - EFC12456 - T1DM

In this T1DM trial, the 6-month change in HbA1c of HOE901-U300 met the noninferiority margin of 0.4% compared to Lantus. Refer to Figure 9 and Table 23 for details.

**Figure 9 - EFC 12456 - Primary Efficacy Endpoint - Mean (+/- SE) in HbA1c (%) by visit during the main 6-month on-treatment period - mITT population**



Source: Figure 3 Study CSR

Figure 9 depicts mean change in HbA1c from baseline (BAS) to month 6 (M6) in both treatment groups. The change in HbA1c mostly occurred in the first 12 weeks of treatment in both groups. The primary efficacy endpoint was the change from BAS (defined as Day 1 -marked the beginning of the randomization period), to month 6. In the sponsor's mixed model with repeat measures (MMRM) analysis, the HbA1c in HOE901-U300 (mean±SD) decreased from a baseline of 8.13%±0.77 to 7.70%±0.99, a difference of -0.42%±0.98 from baseline. In the Lantus, active control group, the HbA1c decreased from (mean±SD) a baseline of 8.12%±0.79 to 7.68%±0.80 a difference of -0.44%±0.72 from baseline. The between drug group LS mean difference±SE was 0.04%±0.072 with a 95% CI of -0.098% to 0.185%. The upper bound of the 95% CI (0.185%) was below the margin of 0.4%, thus meeting the prespecified non-inferiority margin. However, there was a greater numerical decrease in HbA1c in the Lantus group compared to the HOE901-U300 group.

**Table 23 - EFC12456 - Primary efficacy analysis - Mean change in HbA1c (%) from baseline to Month 6 using MMRM analysis - mITT population**

	<b>HOE901-U300</b>	<b>Lantus</b>
<b>HbA1c (%)</b>	<b>Overall</b>	<b>Overall</b>
	<b>(N=273)</b>	<b>(N=273)</b>
<b>Baseline</b>		
Number	247	252
Mean (SD)	8.13 (0.77)	8.12 (0.79)
<b>Month 6 Endpoint (MMRM)</b>		
Number	225	229
Mean (SD)	7.70 (0.99)	7.68 (0.80)
<b>Change from baseline to Month 6 Endpoint (MMRM)</b>		
Number	225	229
Mean (SD)	-0.42 (0.98)	-0.44 (0.72)
LS Mean (SE)	-0.40 (0.051)	-0.44 (0.051)
95% CI	(-0.501 to -0.299)	(-0.543 to -0.344)
LS Mean difference (SE) vs. Lantus	0.04 (0.072)	
95% CI	(-0.098 to 0.185)	

Source: study CSR table 14

EFC 12456 - Mean daily insulin dosage (basal, prandial, and total)

In order to interpret the efficacy results, the reviewer evaluated the mean daily insulin dosage as well as the titration of insulin during the 6-month main study period. Table 24 shows that for both HOE901-U300 and Lantus after an initial lowering of insulin (basal, prandial, and total) from prior to randomization to baseline, there was an increase of prandial and basal insulin over 6 months of treatment. The initial decline in dose from the period prior to randomization to baseline was clarified by the Sponsor in an information response on November 26, 2013. In T1DM patients using basal insulin once daily prior to the study, the starting doses of both HOE901-U300 and Lantus were approximately 15% to 18% lower than the pre-study daily basal insulin dose (morning injection group: approximately 20% in both, HOE901-U300 and Lantus group; evening injection group approximately 10% decrease in both treatment groups).

**Reviewer’s comments: Despite the lack of adherence to a 1:1 conversion in patients transitioned from once daily insulin to HOE901-U300, (i.e. instead there were dose decreases of 10-20%), over the course of the study, there was an overall increase of insulin doses. Hence, it appears that if the 1:1 conversion (without a dose decrease) was followed, these doses would still be close to the Month 6 dose that was achieved in the study.**

**Table 24 – EFC12456 - Mean daily insulin doses**

	HOE901-U300 Mean total daily insulin dose			Lantus Mean total daily insulin dose		
	7 days prior randomization	Baseline	Month 6	7 days prior randomization	Baseline	Month 6
Basal	33.5 U 0.39 U/kg	27.5 U 0.32 U/kg	40.5 U 0.47 U/kg	31.5 U 0.38 U/kg	26.9 U 0.32 U/kg	34.1 U 0.40 U/kg
Prandial	28.1 U 0.34 U/kg	26.4 U 0.32 U/kg	28.7 U 0.34 U/kg	27.1 U 0.33 U/kg	25 U 0.31U/kg	27.1 U 0.33 U/kg
Total	61.9 U 0.73 U/kg	54 U 0.64 U/kg	69.6 U 0.81 U/kg	59.9 U 0.74 U/kg	51.1 U 0.64 U/kg	60.9 U 0.73 U/kg

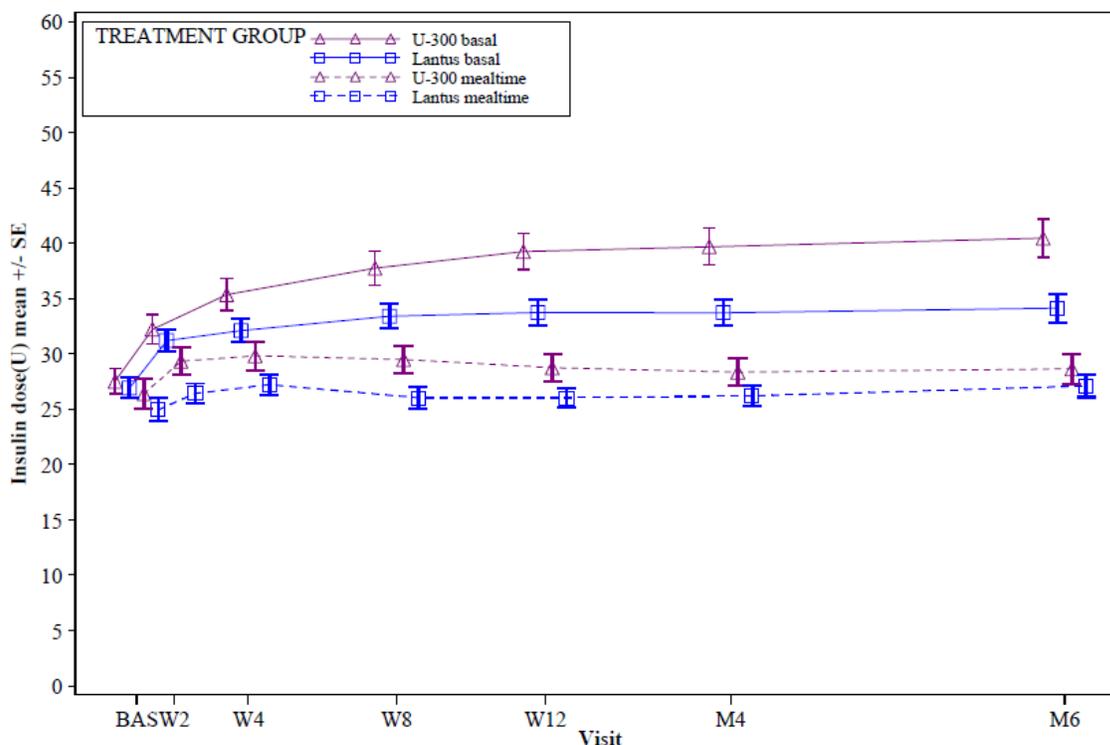
Source: adapted from Study CSR

Refer to Table 12 for details regarding changes in insulin dosage from baseline to Month 6. At baseline, the HOE901-U300 arm required 2.9 greater units of total insulin compared to the Lantus group. In both treatment arms, the basal and bolus ratio was 1:1.

At Month 6, the HOE901-U300 group required 6.4 more units of basal insulin and 1.6 more units of prandial insulin compared to the Lantus group. Overall, the HOE901-U300 group required 8.7 more units of total insulin compared to the Lantus group.

Figure 10 depicts that over the study visits, **both** the basal and prandial insulin doses were always higher in the HOE901-U300 group than in the Lanus group.

**Figure 10 - EFC12456 - Mean (+/- SE) average daily basal and mealtime insulin dose (U) by visit during the main 6-month on-treatment period - mITT population**



# subjects	BASW2	W4	W8	W12	M4	M6
U-300 basal	270	256	246	241	235	225
Lantus basal	271	258	249	239	233	228
U-300 mealtime	213	250	243	239	234	223
Lantus mealtime	193	249	245	234	234	224

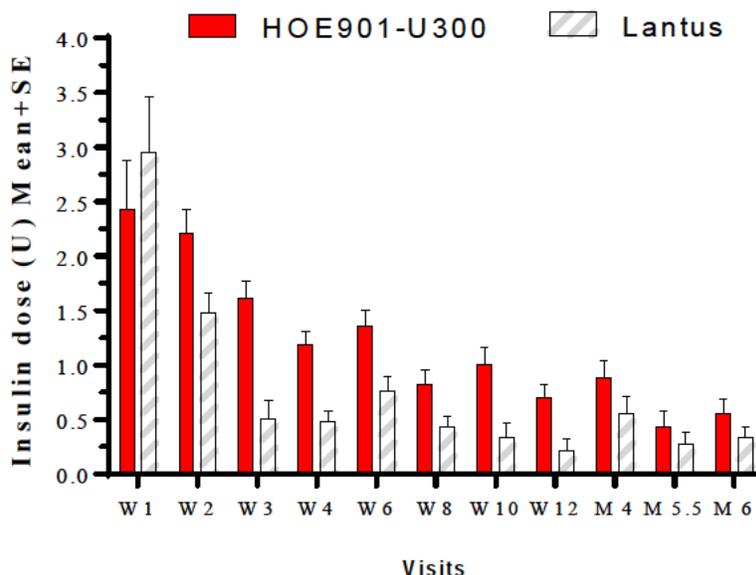
Source: Study CSR Figure 10

The Sponsor’s analysis of titration shows that HOE901-U300 required titration over longer time and higher doses than Lantus (see Figure 11). The titration of Lantus sharply declines by week 3 and then remains close to 0.5 U for the remainder of the study period. The insulin titration of HOE901-U300 declines from week 1 to week 12.

Prandial insulin titration (not shown in this review) was similar throughout the duration of the main 6-month on-treatment period between HOE901-U300 and Lantus.

Refer to Table 7 for details regarding minimum titration allowable by pen.

**Figure 11 – EFC12456 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on treatment period mITT population**



Note: for each visit the mean change from previous visit is displayed (examples : “W1” represents the change in insulin Dose between “Week1” and “Baseline” visits; “M4” represents the change in insulin Dose between “Month 4” and “Week 12” visits)

Source: Reviewer generated graph from Sponsor provided data

**Reviewer’s comment:**

**Higher HOE901-U300 basal and prandial doses with greater dosage titration were needed to reach a change in HbA1c at month 6 that was slightly lower in the HOE901-U300 group (-0.42) than the Lantus group (-0.44). These data are consistent with the finding from Clinical Pharmacology studies that HOE901-U300 has a lesser pharmacodynamic effect than Lantus (see Table 23).**

**These data also suggest that Lantus may have a shorter titration period than HOE901-U300.**

Sensitivity Analyses of the Primary Endpoint

During the 6-month treatment period, dropout rates were similar between the two groups, 15.7% and 14.2% in the HOE901-U300 overall group and Lantus groups respectively. Three sensitivity analyses to evaluate the effect of missing data on the change in HbA1c after 6 months of treatment with the IMP were performed by the Sponsor. These analyses included use of LOCF values as HbA1c endpoints, Month 6 completer population analysis, and a penalized LOCF analysis. All sensitivity analysis showed similar findings to the primary analysis.

**6.1.4.1.2 Secondary efficacy endpoints - EFC12456 – T1DM**

There were no main secondary endpoints specified in this trial. Hence, the reviewer presents the secondary endpoints that may have the most clinical relevance. Overall, results of the pre-specified secondary endpoints of this trial, (see section 5.3 *Discussion of Individual*

*Studies/Clinical Trials* for details), were (b) (4) (see Table 25).

**Table 25 – EFC12456 – Selected secondary efficacy endpoints – Number (%) of patients – mITT population**

(b) (4)



**Reviewer's comments:** (b) (4)



Table 26 shows another secondary efficacy endpoint, the change in fasting plasma glucose from baseline to Month 6.

**Table 26 - EFC12456 - Secondary efficacy endpoint- Summary of mean change in FPG (mg/dL) from baseline to endpoint (Month 6) using MMRM analysis- mITT population**

FPG (mg/dL)	HOE901-U300 Overall (N=273)	Lantus Overall (N=273)
Baseline		
Number	234	236
Mean (SD)	185.86 (76.18)	199.27 (79.58)
Median	174.87	188.18
Min : Max	50.0 : 436.0	43.2 : 542.0
Month 6 Endpoint (MMRM)		
Number	213	216
Mean (SD)	175.47 (71.38)	173.49 (69.36)
Median	164.00	167.50
Min : Max	44.0 : 377.0	47.0 : 409.0
Change from baseline to Month 6 Endpoint (MMRM)		
Number	213	216
Mean (SD)	-7.55 (94.63)	-26.05 (95.13)
Median	-7.00	-22.31
Min : Max	-268.0 : 258.0	-311.7 : 276.0
LS Mean (SE) <sup>a</sup>	-17.09 (4.730)	-20.54 (4.678)
95% CI	(-26.382 to -7.790)	(-29.730 to -11.342)
LS Mean difference (SE) vs. Lantus <sup>a</sup>	3.45 (6.669)	
95% CI	(-9.657 to 16.558)	

FPG=Fasting Plasma Glucose

MMRM = Mixed model for repeated measurements

<sup>a</sup>MMRM analysis with randomized groups (HOE901-U300 Morning injection, HOE901-U300 Evening injection, Lantus Morning injection and Lantus Evening injection), randomization strata of screening HbA1c (<8.0, ≥8.0%), randomization strata of geographical region (Non Japan; Japan), visit (Week 12, Month 6) and visit-by-randomized groups interaction as fixed categorical effects as well as baseline FPG value and baseline FPG-by-visit interaction as continuous fixed covariates.

MMRM value is either the observed value at selected visit or value retrieved according to time windows defined in the SAP

Source: Study CSR-Table 22

**Reviewer’s comments: Despite the decrease in FPG from baseline in both groups, Lantus had a slightly greater decrease in FPG than the HOE901-U300 group. These data are consistent with primary efficacy analysis.**

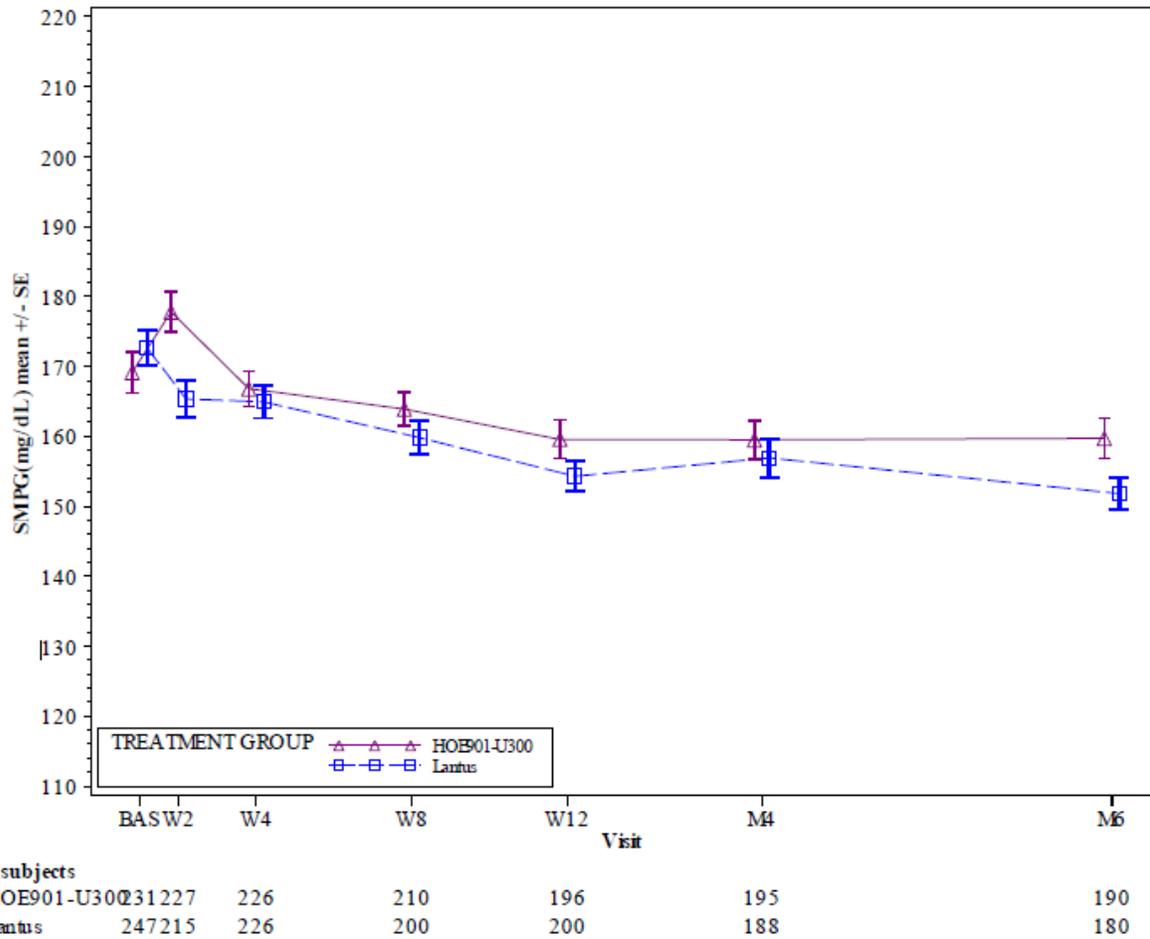
#### 6.1.4.1.3 Other Endpoints - EFC12456 – T1DM

##### EFC12456 - SMPG measures

SMPG 24-hour average plasma glucose results (from 8-point SMPG profiles); show that there was a transient increase in SMPG values in the HOE901-U300 compared to the Lantus group at

Week 2. Overall, it appears that SMPG values were higher for HOE901-U300 compared to Lantus, during the duration of the main 6-month on-treatment period.

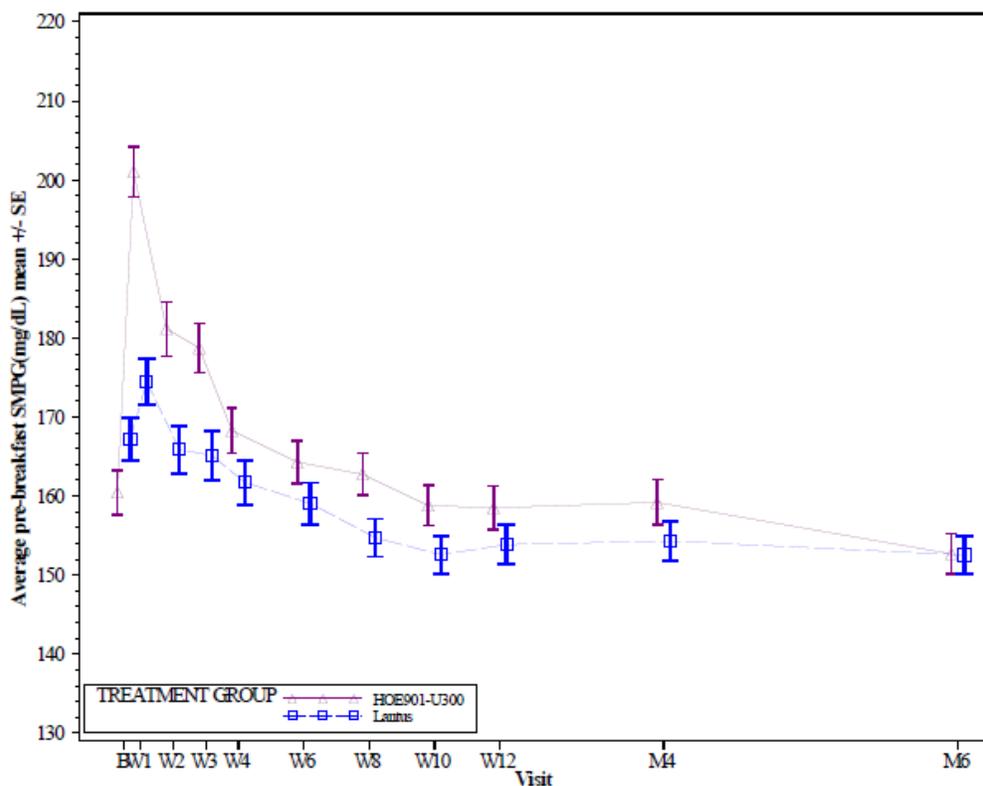
**Figure 12 – EFC12456 - 24-hour average plasma glucose based on 8-point profile SMPG (mg/dL; mean ± SE) by visit (main 6-month on-treatment period; mITT population)**



Source: study CSR, Appendix 16.2.6.2.8.9.1

Similar findings were seen in the average pre-breakfast SMPG values during the 6-month on treatment period.

**Figure 13 – EFC12456 - Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period**



Source: Sponsor response Nov 26, 2014

**Reviewer’s comment:** Glucose data from glucometers are usually less reliable than centrally obtained and analyzed plasma glucose. Although this data can be considered exploratory, both the 8-point SMPG and pre-breakfast SMPG data are consistent with the Clinical Pharmacology findings of a decreased pharmacodynamic effect of HOE901-U300 compared to Lantus and possibly also represent the observed lag time to onset of action of HOE901-U300. These data suggest a potential risk for early hyperglycemia upon switching from other insulins to HOE901-U300, although the maximum SMPG value appears to only reach 200 mg/dL. See 7.3.5 *Submission Specific Primary Safety Concerns* for further details regarding the risk of early hyperglycemia when switching to HOE901-U300.

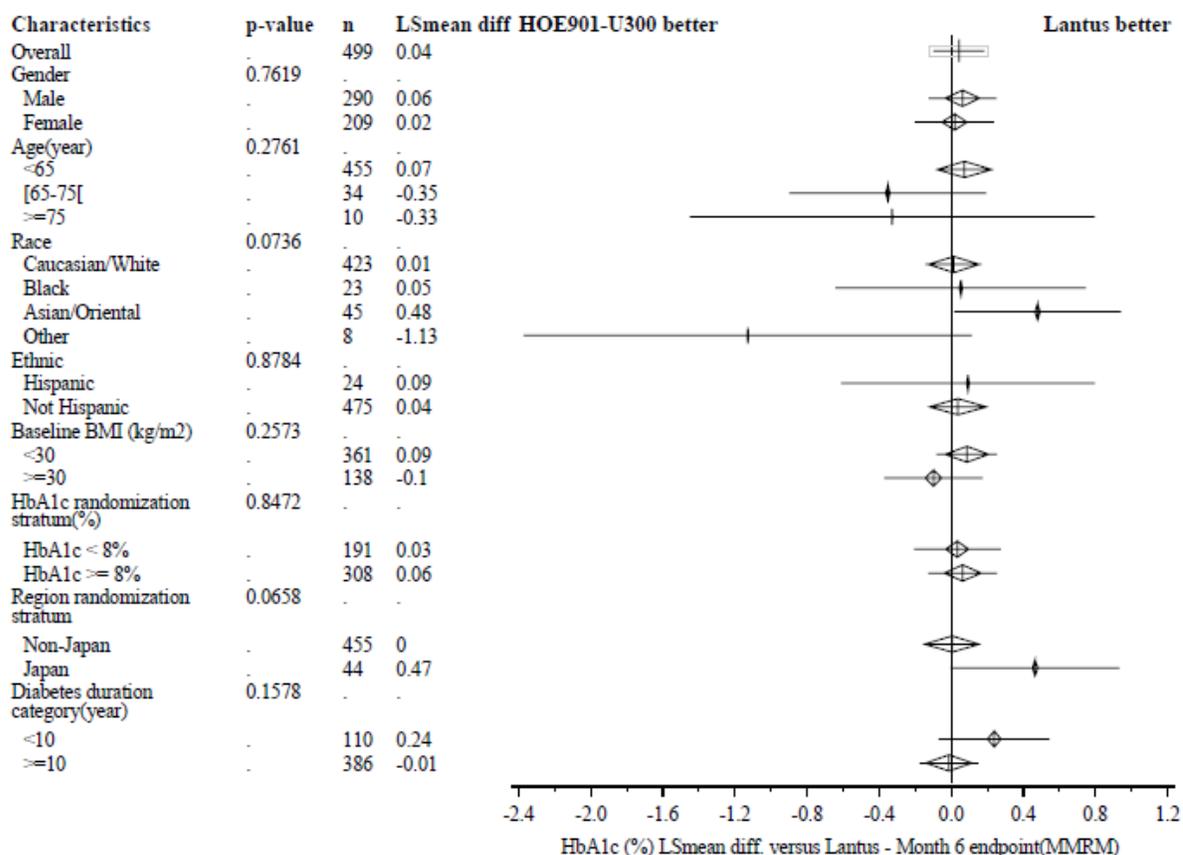
EFC 12456 – T1DM - Analysis of body weight

After 6 months of treatment, the HOE901-U300 overall group had a mean (SD) increase in body weight of +0.46 (3.15) kg versus +1.02 (3.08) kg in the Lantus overall group.

**Reviewer is Comments:** Weight gain is often seen with use of insulin in the treatment of diabetes. Despite greater insulin concentration (U/kg) use in the HOE901-U300 overall group, there was less weight gain observed than Lantus overall group. However, the observed difference was very small and not clinically meaningful.

#### 6.1.4.1.4 Subpopulations - EFC12456 – T1DM

**Figure 14 - Subgroup analyses on primary efficacy endpoint- Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using MMRM analysis by baseline characteristics- mITT population**



MMRM = Mixed model for repeated measurements

BMI= body mass index.

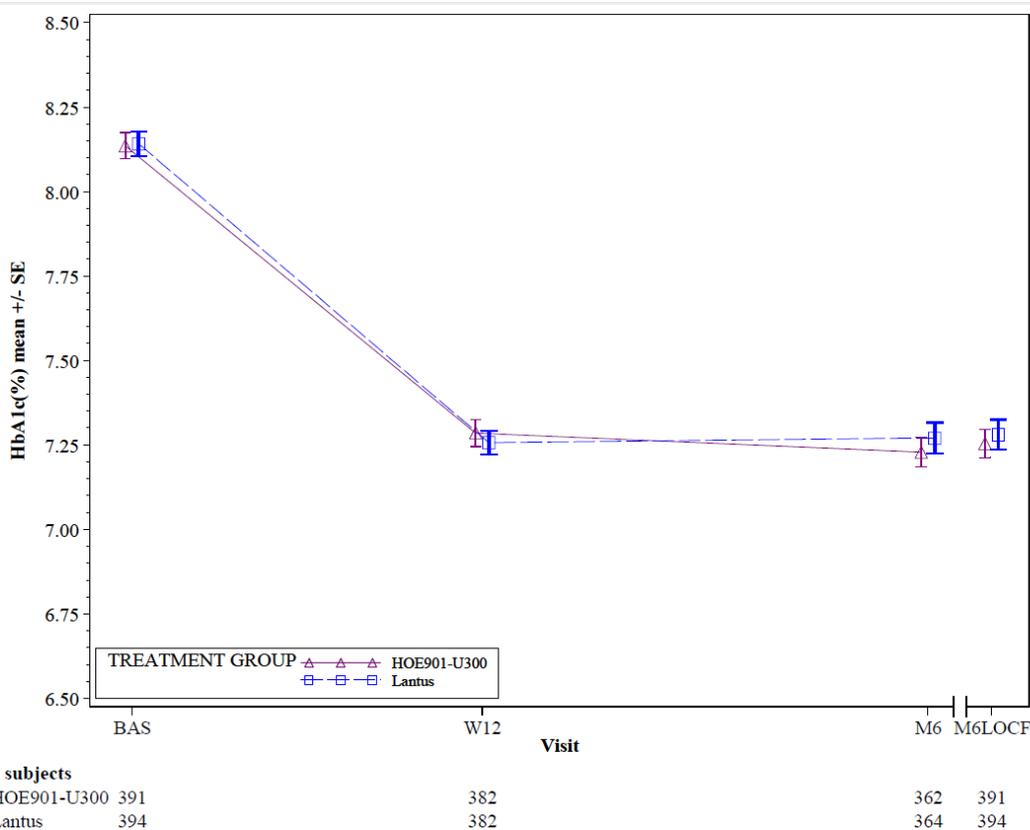
<sup>a</sup>subgroup p-values assessing randomized group-by-factor interaction come from a MMRM analysis with randomized groups (HOE901-U300 Morning injection, HOE901-U300 Evening injection, Lantus Morning injection, Lantus Evening injection), randomization strata of screening HbA1c (<8.0, ≥ 8.0%), subgroup factor, visit (week 12, Month 6), visit-by-randomized group interaction, subgroup factor-by-randomized group, subgroup factor-by-visit-interaction and subgroup factor-by-randomized group-by-visit interaction as fixed categorical effects as well as baseline HbA1c value and baseline HbA1c-by-visit interaction as continuous fixed covariate. HbA1c baseline value and baseline HbA1c-by-visit interaction are removed from the model when HbA1c stratum is used as subgroup factor.]

The Sponsor's analysis of treatment effect (mean change in HbA1c from baseline to endpoint [Month 6]) by HOE901-U300 overall versus Lantus overall was consistent across subgroups. All analyses had nonsignificant p-values at 0.05 for treatment-by-subgroup interactions. The largest confidence intervals were seen in the subpopulations that were minimally represented in the study (such as patients older than 75 years of age, and non-White groups).

### 6.1.4.2.1 Primary efficacy endpoint - EFC11628 – T2DM patients taking IMP plus meal time insulin

The primary efficacy endpoint was the change in HbA1c from baseline to month 6 analyzed using an analysis of covariance (ANCOVA) model. In this T2DM trial, the 6-month change in HbA1c by HOE901-U300 met the noninferiority margin of 0.4% compared to Lantus. Refer to Figure 15 and Table 27 for details.

**Figure 15 - EFC11628 - Main efficacy analysis – Mean HbA1c (%) by visit during the main 6-month on-treatment period - mITT population**



BAS = Baseline, M6LOCF= Month-6 endpoint (LOCF)  
LOCF = Last observation carried forward.  
Source: Study CSR

Figure 15 depicts the mean change in HbA1c from baseline (BAS) to month 6 (M6) in both treatment groups. The change in HbA1c occurred mostly in the first 12 weeks of treatment in both groups. The primary efficacy endpoint was the change from BAS (defined as Day 1-, which marked the beginning of the randomization period) to month 6. In the Sponsor’s analysis, the HbA1c in HOE901-U300 (mean±SD) decreased from a baseline of 8.14%±0.78 to 7.25%±0.85; LS mean (SE) difference of -0.83±0.06 from baseline. In the Lantus active control

group, the HbA1c decreased from (mean±SD) a baseline of 8.14%±0.76 to 7.28%±0.92 an LS mean (SE) difference of -0.83±0.061 from baseline. The between drug group LS mean difference±SE was 0.00%±0.056 with a 95% CI of -0.112% to 0.107%. The upper bound of the 95% CI (0.107%) was below the margin of 0.4%, thus meeting the prespecified non-inferiority margin. At the completion of the 6-month period, there was close to no difference in HbA1c change between the two groups.

**Table 27 - EFC11628 - Main efficacy analysis - Mean change in HbA1c from baseline to endpoint (Month 6) using LOCF procedure – mITT population**

HbA1c (%)	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
Number	391	394
Mean (SD)	8.14 (0.78)	8.14 (0.76)
Median	8.10	8.10
Min : Max	6.5 : 10.6	6.4 : 10.3
Month 6 endpoint (LOCF)		
Number	391	394
Mean (SD)	7.25 (0.85)	7.28 (0.92)
Median	7.10	7.20
Min : Max	5.3 : 10.6	5.2 : 13.8
Change from baseline to Month 6 endpoint (LOCF)		
Number	391	394
Mean (SD)	-0.88 (0.81)	-0.86 (0.92)
Median	-0.90	-0.90
Min : Max	-3.4 : 1.8	-3.1 : 4.6
LS Mean (SE) <sup>a</sup>	-0.83 (0.060)	-0.83 (0.061)
95% CI	(-0.946 to -0.709)	(-0.944 to -0.706)
LS Mean difference (SE) vs. Lantus <sup>a</sup>	-0.00 (0.056)	
95% CI	(-0.112 to 0.107)	

LOCF = Last observation carried forward.

<sup>a</sup>Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%) and country as fixed effects and baseline HbA1c value as covariate.

Source: Study CSR Table 14

#### EFC11628- Mean daily insulin dosage

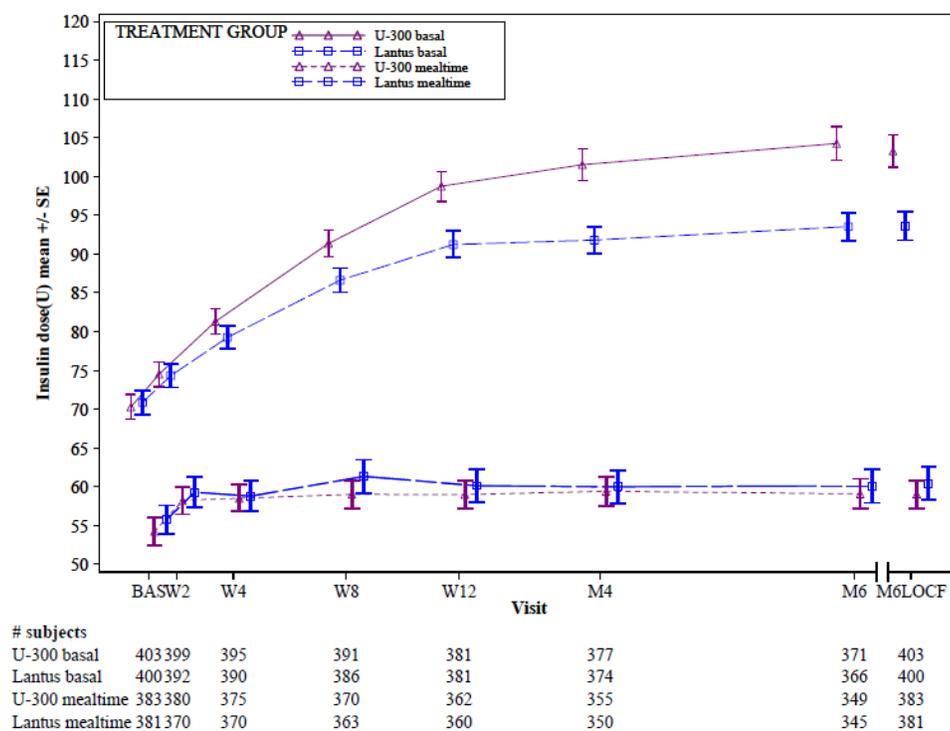
In order to interpret the efficacy results, the reviewer evaluated the mean daily insulin dosage as well as the titration of insulin during the 6-month main study period.

Refer to Table 12 for details regarding changes in dosage from baseline to Month 6. At baseline, the HOE901-U300 arm required 1.5 units less of total insulin compared to the Lantus group.

At Month 6, the HOE901-U300 group required 9.6 units more of basal insulin and 1.4 units less of prandial insulin compared to the Lantus group. Overall, Table 12 shows that the HOE901-U300 group required 8.8 more units of total insulin compared to the Lantus group (a percent unit/kg difference of 7.7%).

Figure 16 depicts that over the study visits, the basal insulin doses were always higher in the HOE901-U300 group than the Lantus group, while maintaining similar prandial doses in both groups.

**Figure 16 - EFC11628-Average daily basal insulin and mealtime insulin dose (U) by visit during the main 6-month on-treatment period - mITT population**

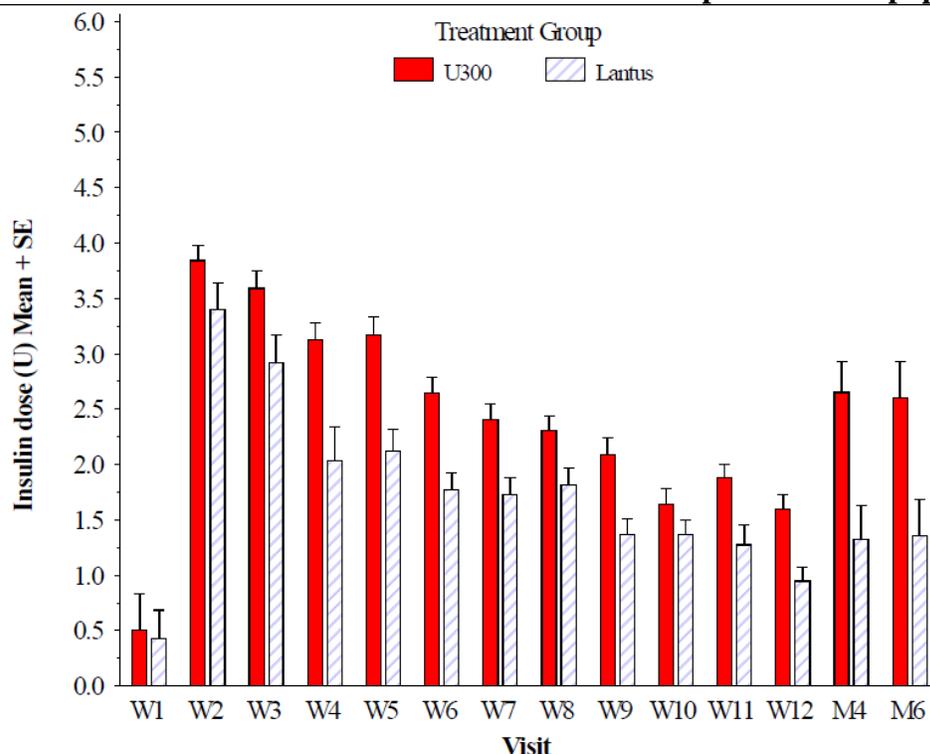


Source: Study CSR, Figure 10

The Sponsor’s analysis of titration (by visit) shows that HOE901-U300 was titrated at higher insulin doses than Lantus at every study visit. Beyond week 12 (M4 and M6), both insulins are again titrated up, with again HOE901-U300 requiring higher dose titration (see Figure 17). Prandial insulin titration (not shown in this review) was similar throughout the duration of the main 6-month on-treatment period between HOE901-U300 and Lantus.

Refer to Table 7 for details regarding minimum titration allowable by the pen devices used in the trial.

**Figure 17 – EFC11628 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on –treatment period mITT population**



Note: for each visit the mean change from previous visit is displayed (examples : “W1” represents the change in insulin Dose between “Week1” and “Baseline” visits; “M4” represents the change in insulin Dose between “Month 4” and “Week 12” visits)

Source: Sponsor’s response to information request.

**Reviewer’s comment:**

**The higher HOE901-U300 basal doses and the greater dosage titration at each visit, to reach similar change in HbA1c at month 6 is again, consistent with the observation that HOE901-U300 has a decreased pharmacodynamic effect compared to Lantus on a unit to unit basis.**

**The difference between basal insulin doses (when comparing Month 6 values: HOE901-U300 – Lantus) approaches 9.6 units. The benefit of decreased volume associated with HOE901-U300 is also undermined, since greater doses (and hence greater volume) are needed to achieve glycemic control (although volume per dose remains lower than Lantus).**

Sensitivity Analyses of the Primary Endpoint

Over 90% of participants in each drug treatment completed the 6-month treatment phase. The Sponsor performed three sensitivity analyses to assess the impact of missing data on the conclusion of the primary analysis: 1) an analysis using a Mixed-effect Model for Repeated Measures (MMRM), 2) a penalized LOCF analysis, and 3) an analysis on the Month-6 completer population. All sensitivity analyses supported the limited impact of missing data on the primary efficacy analysis results.

**6.1.4.2.2 Secondary efficacy endpoints - EFC11628 – T2DM**

The Sponsor followed the hierarchical testing procedure (specified in SAP, see 5.3 *Discussion of Individual Studies/Clinical Trials* for details), to evaluate for superiority, adjusting for multiplicity, of HOE901-U300 for the main secondary endpoints. (b) (4)

**Table 28 - EFC11628 - Incidence of patients (%) with at least one severe and/or confirmed nocturnal hypoglycemia (plasma glucose  $\leq$  70 mg/dL) between hours of 00:00 and 05:59 during month 3 to month 6**

(b) (4)

**Reviewer's comments:**

**As mentioned throughout this review, the clinical significance of this secondary endpoint is questionable** (b) (4)

(b) (4)

See Table 29 below for secondary endpoints, which further characterize the glycemic control of both HOE901-U300 vs. Lantus.

**Table 29 - EFC11628 - Selected secondary efficacy endpoints - Number (%) of patients – mITT population**

(b) (4)



**Reviewer's comments:**

(b) (4)



Table 30 shows the change in fasting plasma glucose from baseline to Month 6. In both treatment groups, FPG declined mostly in the first 12 weeks of therapy.

**Table 30 - EFC11628 - Mean change in FPG (mg/dL) from baseline to Month 6 using LOCF procedure - mITT population**

FPG (mg/dL)	HOE901-U300 (N=404)	Lantus (N=400)
Baseline		
Number	376	385
Mean (SD)	157.05 (51.05)	160.37 (52.95)
Median	151.32	154.93
Min : Max	41.4 : 345.9	43.2 : 374.7
Month 6 endpoint (LOCF)		
Number	376	385
Mean (SD)	130.42 (46.22)	129.97 (43.29)
Median	122.50	124.30
Min : Max	43.2 : 327.9	48.6 : 317.1
Change from baseline to Month 6 endpoint (LOCF)		
Number	376	385
Mean (SD)	-26.63 (56.00)	-30.40 (57.89)
Median	-25.22	-30.63
Min : Max	-246.8 : 203.6	-225.2 : 162.1
LS Mean (SE) <sup>a</sup>	-23.23 (3.449)	-24.89 (3.452)
95% CI	(-29.996 to -16.456)	(-31.663 to -18.110)
LS Mean difference (SE) vs. Lantus <sup>a</sup>		
95% CI	1.66 (3.083)	(-4.392 to 7.714)

FPG=Fasting Plasma Glucose

LOCF = Last observation carried forward.

<sup>a</sup>Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%) and country as fixed effects and baseline FPG value as covariate.

Source: Study CSR Table 22

**Reviewer’s comment:**

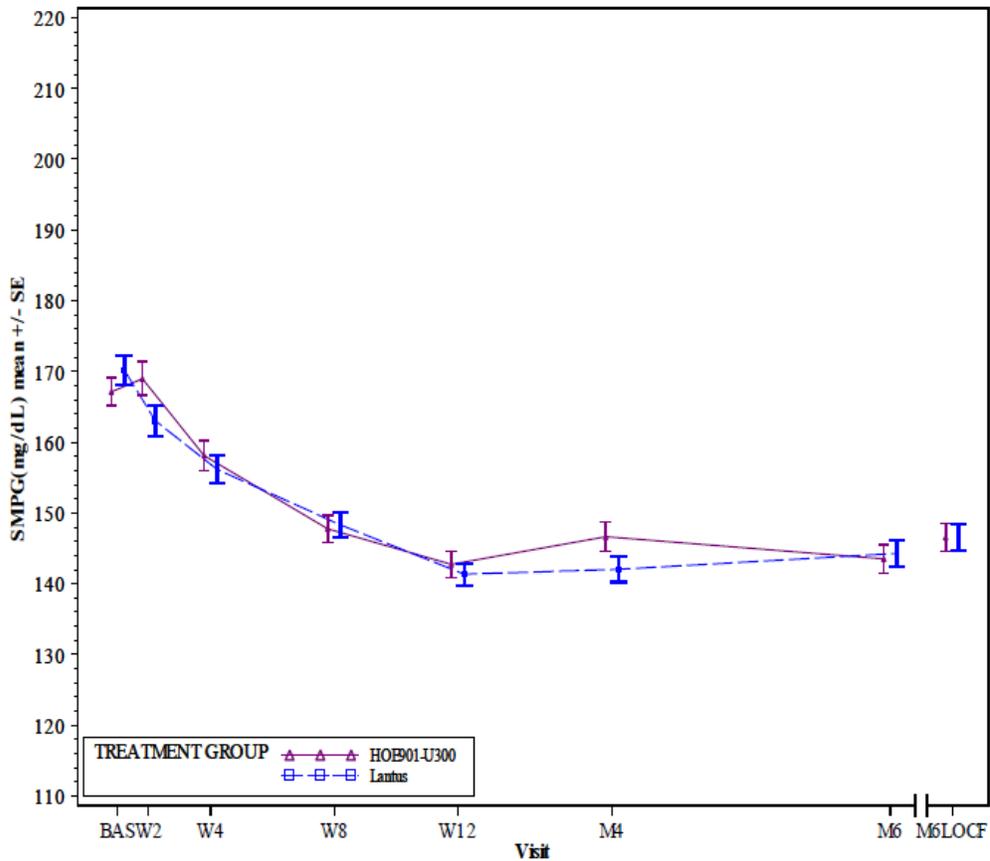
**The small numerical difference in in FPG, favoring Lantus does not result in a clinically meaningful difference.**

**6.1.4.2.3 Other Endpoints - EFC11628 – T2DM**

EFC11628 – SMPG measures

SMPG 24- hour average plasma glucose results (from 8-point SMPG profiles), show that there was a transient increase in SMPG values in the HOE901-U300 compared to the Lantus group at Week 2. SMPG values decrease similarly between the two groups up to Week 12.

**Figure 18 – EFC11628- 24-hour average plasma glucose based on 8-point profile SMPG (mg/dL; mean ± SE) by visit (main 6-month on-treatment period; mITT population)**

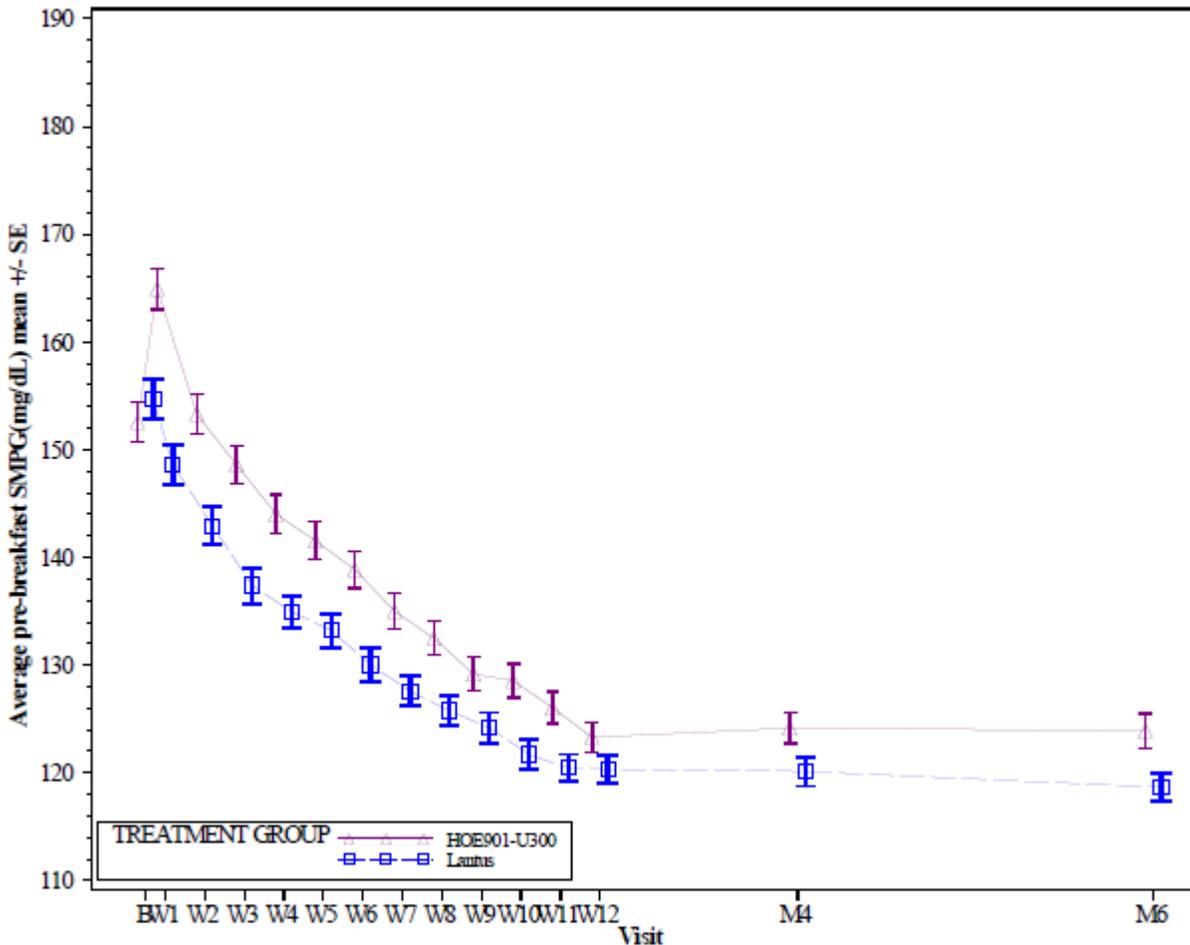


# subjects	BASW2	W4	W8	W12	M4	M6	M6LOCF
HOE901-U300	43308	302	303	296	287	278	343
Lantus	334299	297	296	294	263	270	334

Source: CSR, Appendix 16.2.6.3.6.7.1

Similar findings were seen in the average pre-breakfast SMPG values during the 6-month on treatment period. Although, higher pre-breakfast SMPG values were seen in the HOE901-U300 group compared to the Lantus group.

**Figure 19 - EFC11628 - Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period**



**Reviewer's comment:** The higher HOE901-U300 SMPG values (both from pre-breakfast and 8-point readings), at Week 2, are consistent with the pattern seen in other studies (EFC12456). Again, see 7.3.5 Submission Specific Primary Safety Concerns for further details regarding the risk of early hyperglycemia when switching to HOE901-U300.

EFC11628- Body weight

At Month 6, there was an increase in body weight in both treatment groups from a baseline of (mean±SD) 106.11±21.43 to 107.04±21.86 in the HOE901-U300 group and 106.5±19.94 to 107.4±20.33 in the Lantus group. The change from baseline to Month 6 by LOCF was +0.93 in the HOE901-U300 and +0.90 in the Lantus group.

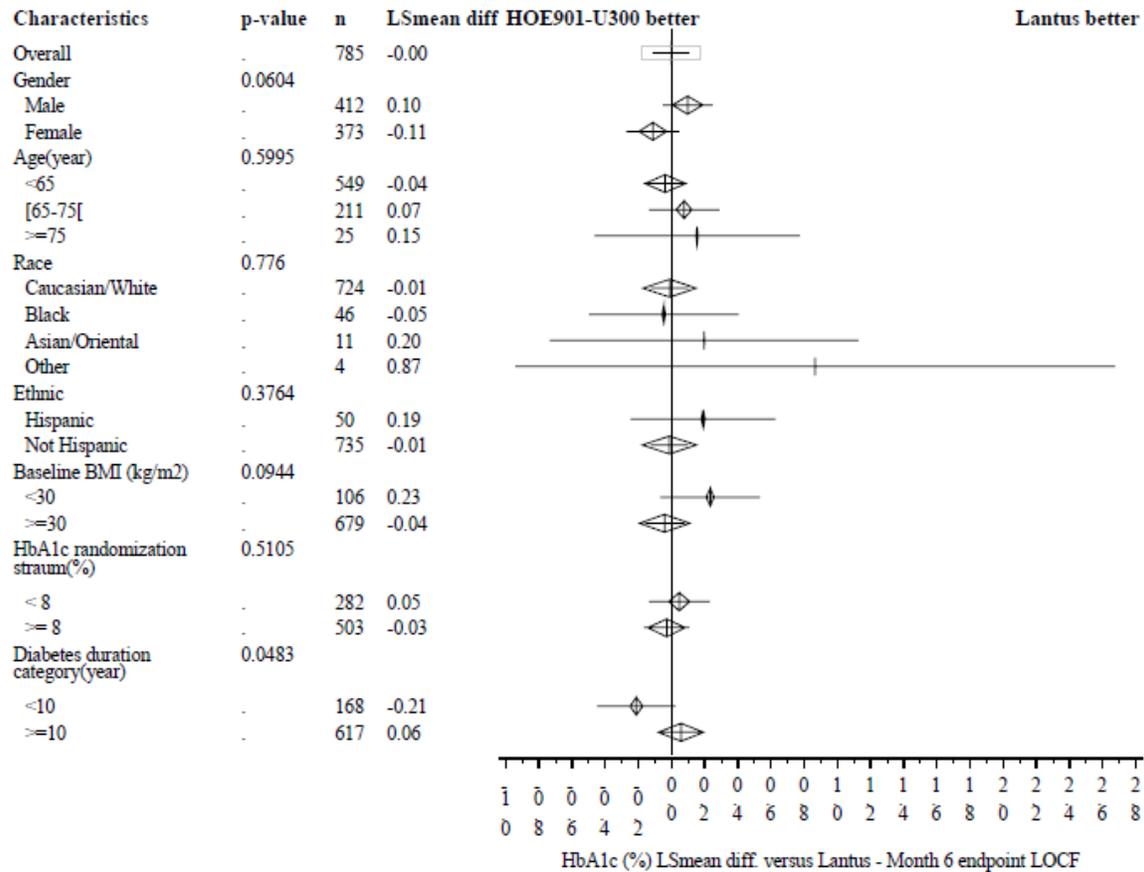
**Reviewer's comments:** Despite higher total insulin doses (mostly made up by basal doses), in the HOE901-U300, there was similar weight gain observed in both the HOE901-U300 and Lantus, after 6 months of treatment.

#### **6.1.4.2.4 Subpopulations - EFC11628 –T2DM**

Overall the treatment effect of HOE901-U300 versus Lantus was consistent across tested subgroups. No significant treatment-by-subgroup interaction was observed at the 5% level, except for duration of diabetes. Patients with diabetes for <10 years had an LS mean difference between HOE901-U300 and Lantus of HbA1c of -0.21 (i.e. favors HOE901-U300) compared to those with diabetes duration of greater than or equal to 10 years (with an LS mean difference between HOE901-U300 and Lantus of +0.06 (i.e. slightly favors Lantus), p for interaction=0.0483).

**Reviewer’s comment: the clinical significance of this finding is unclear; I believe this is due to chance.**

**Figure 20 – Subgroup analyses on primary efficacy endpoint – Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using LOCF procedure by baseline characteristics - mITT population**



LOCF = Last observation carried forward.

BMI= body mass index.

<sup>a</sup>subgroup p-values assessing treatment-by-factor interaction come from analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and

LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%), country, subgroup and its interaction- by-treatment group as fixed effects and baseline

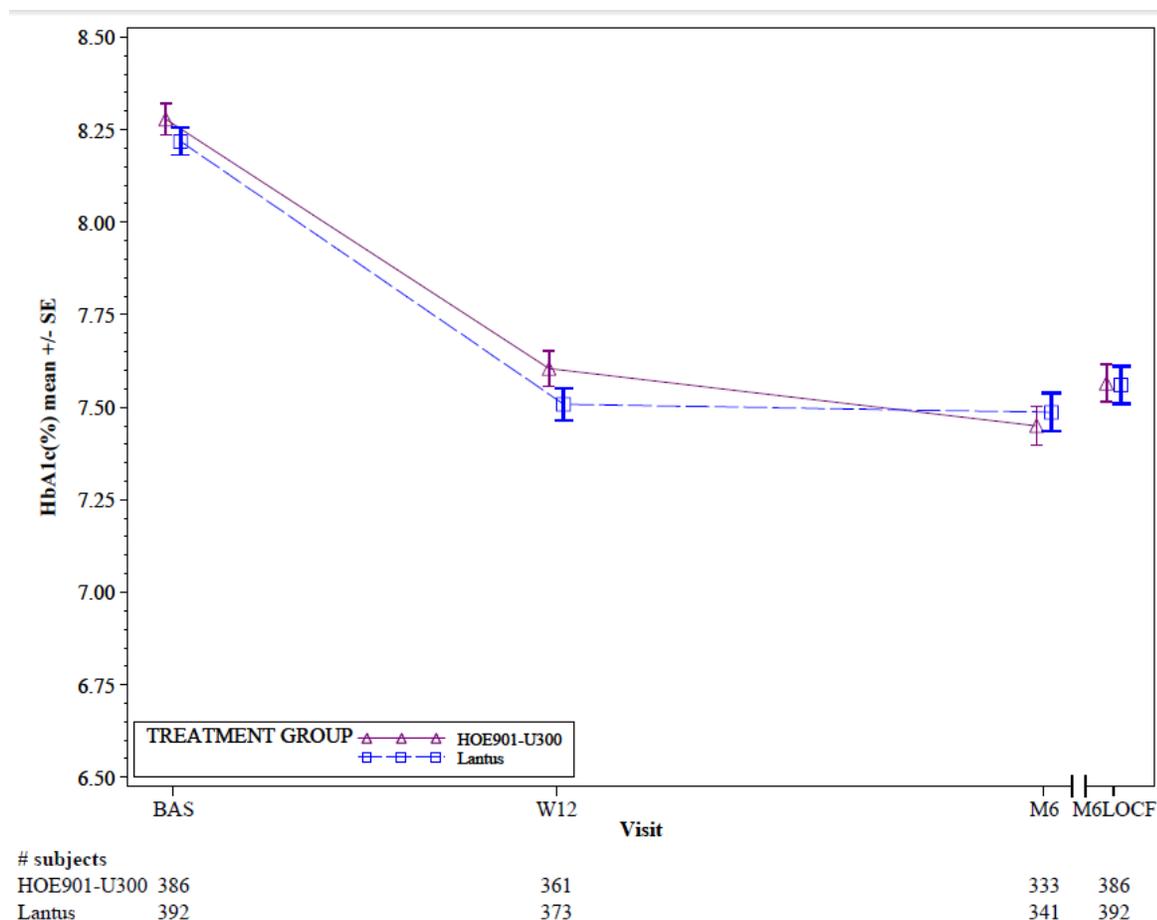
HbA1c value as covariate. HbA1c randomisation strata is removed from the model when HbA1c stratum is used as baseline factor.

Source: Study CSR, figure 4

### 6.1.4.3.1 Primary efficacy endpoint - EFC11629 - T2DM patients taking oral antihyperglycemic drugs(s) (OADs)

In this T2DM trial, the 6-month change in HbA1c met the noninferiority margin of 0.4% compared to Lantus. Refer to Figure 21 and Table 31 for details.

**Figure 21 - EFC11629 -Main efficacy analyses-Mean HbA1c (%) by visit during the main 6-month on-treatment period-mITT population**



BAS = Baseline, M6LOCF= Month-6 endpoint (LOCF)  
LOCF = Last observation carried forward.  
Source: Study CSR Figure 3

Figure 21 depicts mean change in HbA1c from baseline (BAS) to month 6 (M6) in both treatment groups. Most of the change in HbA1c occurred in the first 12 weeks of treatment in both groups. The primary efficacy endpoint was the change from BAS (defined as Day 1 - marked the beginning of the randomization period), to month 6. The Sponsor's analysis showed a decrease in HbA1c in HOE901-U300 (mean±SD) from a baseline of 8.28%±0.87 to 7.57%±1.02, a difference of -0.71%±1.05 from baseline. In the Lantus active control group, the HbA1c decreased from (mean±SD) a baseline of 8.22%±0.77 to 7.56%±1.04, a difference of -0.66%±0.90 from baseline. The between drug group LS mean difference±SE (HOE901-U300 vs Lantus) was 0.01%±0.066 with a 95% CI of -0.139% to 0.119%. The upper bound of the 95% CI (0.119%) was below the margin of 0.4%, thus meeting the prespecified non-inferiority margin (See Table 31).

**Table 31 - EFC11629 - Main efficacy analysis - Mean change in HbA1c (%) from baseline to endpoint (Month 6) using LOCF – mITT population**

HbA1c (%)	HOE901-U300 (N=403)	Lantus (N=405)
Baseline		
Number	386	392
Mean (SD)	8.28 (0.87)	8.22 (0.77)
Median	8.20	8.10
Min : Max	6.0 : 12.6	6.7 : 10.4
Month 6 endpoint (LOCF)		
Number	386	392
Mean (SD)	7.57 (1.02)	7.56 (1.04)
Median	7.40	7.50
Min : Max	5.4 : 14.2	5.3 : 12.0
Change from baseline to Month 6 endpoint (LOCF)		
Number	386	392
Mean (SD)	-0.71 (1.05)	-0.66 (0.90)
Median	-0.70	-0.70
Min : Max	-3.9 : 5.3	-3.4 : 3.1
LS Mean (SE) <sup>a</sup>	-0.57 (0.094)	-0.56 (0.093)
95% CI	(-0.756 to -0.387)	(-0.744 to -0.379)
LS Mean difference (SE) vs. Lantus <sup>a</sup>		
95% CI	-0.01 (0.066) (-0.139 to 0.119)	

LOCF = Last observation carried forward.

<sup>a</sup>Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%) and country as fixed effects and baseline HbA1c value as covariate.

Note: For all patients rescued during the 6-month period, the last postbaseline HbA1c measurement before rescue and during the 6-month on-treatment period will be used as the HbA1c endpoint.

Source: Study CSR Table 15

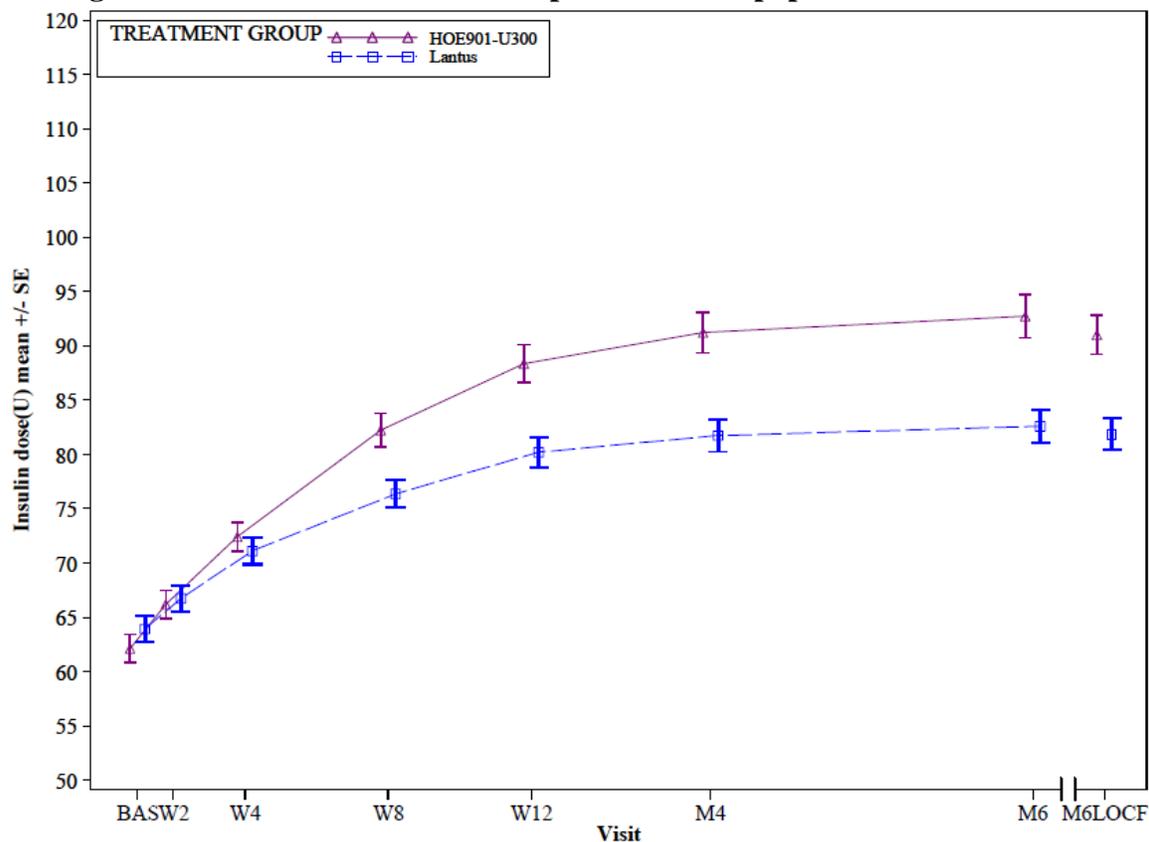
**Reviewer’s comments: In contrast to the other two trials reviewed above, in this trial (T2DM on background of OADs) U300 was numerically better than Lantus, although the difference was very small.**

Study EFC11629- Mean daily basal insulin dosage

Refer to Table 12 for dose change details. The doses of basal insulin doses increased over time in both groups. The dose of insulin in the HOE901-U300 at the endpoint (Month 6) was 91 Units (0.92 U/kg), an increase from 62.1 Units (0.64 U/kg) at baseline. Likewise, Lantus daily dose at the end of Month 6 was 81.9 Units (0.84 U/kg) an increase from 63.9 Units (0.66 U/kg) at baseline.

Figure 22 shows that over the study visits, the basal insulin doses were always higher in the HOE901-U300 group than the Lantus group.

**Figure 22 - EFC11629- Mean (+/- SE) in average daily insulin glargine dose (Units) over time during the main 6-month on-treatment period - mITT population**



# subjects	BASW2	W4	W8	W12	M4	M6	M6LOCF
HOE901-U300	402	396	387	374	363	353	339
Lantus	403	399	392	382	375	355	349
							402
							403

BAS = Baseline, M6LOCF= last value during main 6-month on-treatment (LOCF).

LOCF = Last observation carried forward.

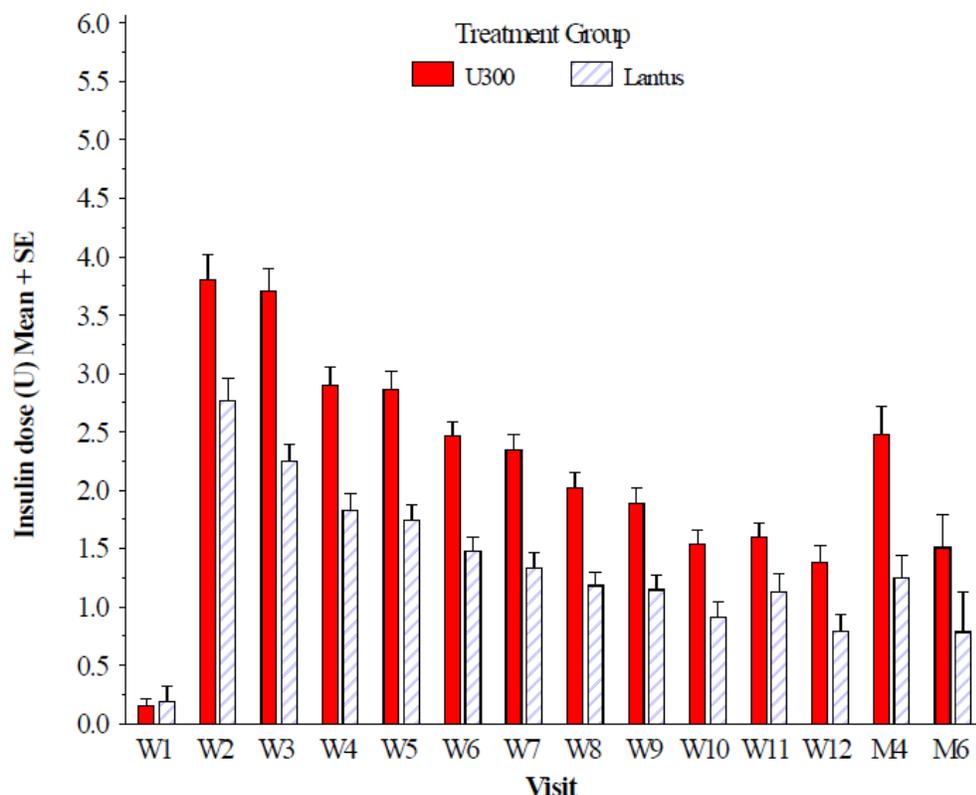
Note: For all patients rescued during the 6-month period, the last postbaseline insulin dose measurement before rescue and during the 6-month on-treatment period will be used as the insulin dose endpoint.

Source: Study CSR, Figure 11

The Sponsor's analysis of titration (by visit) shows that HOE901-U300 was titrated at higher insulin doses than Lantus at every study visit. Beyond the titration period (M4 and M6), increased dose titration was needed for both HOE901-U300 and Lantus (see Figure 23).

Refer to Table 7 for details regarding minimum titration allowable by pen.

**Figure 23 – EFC11629 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on-treatment period in mITT population**



Note: For all patients rescued during the 6-month on-treatment period, only the post-baseline insulin doses before rescue and during the 6-month on-treatment period are considered in the analysis.

Note: for each visit the mean change from previous visit is displayed (examples : “W1” represents the change in insulin Dose between “Week1” and “Baseline” visits; “M4” represents the change in insulin Dose between “Month 4” and “Week 12” visits).

Source: Sponsor, per information request

**Reviewer’s comment: Higher HOE901-U300 doses, with greater dosage titration were needed to reach a similar change in HbA1c at month 6 (HOE901-U300: -0.57 vs. Lantus: -0.56). These data are consistent with the observed pharmacodynamic differences discussed previously.**

#### Sensitivity Analyses of the Primary Endpoint EFC11629

The sensitivity analyses performed by the Sponsor including: the Month 6 completer population, penalized LOCF analysis and analysis performed adjusting by days on concomitant rescue medications using a multilevel model procedure, were all consistent with the primary analysis. The agreement of the sensitivity analysis with the primary efficacy results, suggests that there was minimal contribution of missing data on the primary outcome.

#### **6.1.4.3.2 Secondary endpoints - EFC11629 - T2DM**

The Sponsor followed the hierarchical testing procedure (specified in SAP, see 5.3 Discussion of Individual Studies/Clinical Trials for details), to evaluate for superiority, adjusting for

multiplicity, of HOE901-U300 for the main secondary endpoints. [REDACTED] (b) (4)

**Table 32 - EFC11629 - Number (%) of patients with at least one nocturnal hypoglycemia event occurring between Week 9 and endpoint (Month 6) (using LOCF procedure)**

(b) (4)

**Reviewer's comment: As mentioned throughout this review, the clinical significance of this secondary endpoint is questionable** [REDACTED] (b) (4)

[REDACTED] **Refer to section 7.3.4 *Significant Adverse Events* for further comments regarding hypoglycemia findings in this trial. Refer to section** [REDACTED] (b) (4)

[REDACTED] **for details regarding the Agency's concern.**

See Table 33 for secondary endpoints that further characterize the glycemic control of both HOE901-U300 vs. Lantus.

**Table 33 - EFC11629 - Selected secondary efficacy endpoints –Number (%) if patients-mITT population**

(b) (4)

(b) (4)

**Reviewer's comment:**

(b) (4)

Table 34 shows the change in FPG from baseline to Month 6. In both treatment groups, FPG declined mostly in the first 12 weeks of therapy with a treatment mean difference of HOE901-U300 vs. Lantus of 3.38 mg/dL (95% CI:-2.670 to 9.435).

**Table 34 - EFC11629- Other secondary efficacy endpoints- Mean change in FPG (mg/dL) from baseline to endpoint (month 6) using LOCF procedure - mITT population**

FPG (mg/dL)	HOE901-U300 (N=403)	Lantus (N=405)
Baseline		
Number	375	379
Mean (SD)	148.37 (53.45)	142.17 (48.09)
Median	140.52	133.31
Min : Max	48.6 : 362.1	52.2 : 299.0
Month 6 endpoint (LOCF)		
Number	375	379
Mean (SD)	127.75 (44.56)	123.04 (42.75)
Median	120.70	113.49
Min : Max	52.2 : 439.6	50.4 : 322.5
Change from baseline to Month 6 endpoint (LOCF)		
Number	375	379
Mean (SD)	-20.62 (61.58)	-19.13 (54.34)
Median	-16.21	-16.21
Min : Max	-236.0 : 198.2	-201.8 : 189.2
LS Mean (SE) <sup>a</sup>	-18.49 (4.357)	-21.87 (4.337)
95% CI	(-27.041 to -9.933)	(-30.383 to -13.356)
LS Mean difference (SE) vs. Lantus <sup>a</sup>	3.38 (3.083)	
95% CI	(-2.670 to 9.435)	

FPG=Fasting Plasma Glucose

LOCF = Last observation carried forward.

<sup>a</sup>Analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%) and country as fixed effects and baseline FPG value as covariate.

Note: For all patients rescued during the 6-month period, the last postbaseline FPG measurement before rescue and during the 6-month on-treatment period will be used as the FPG endpoint.

Source: Study CSR Table 22

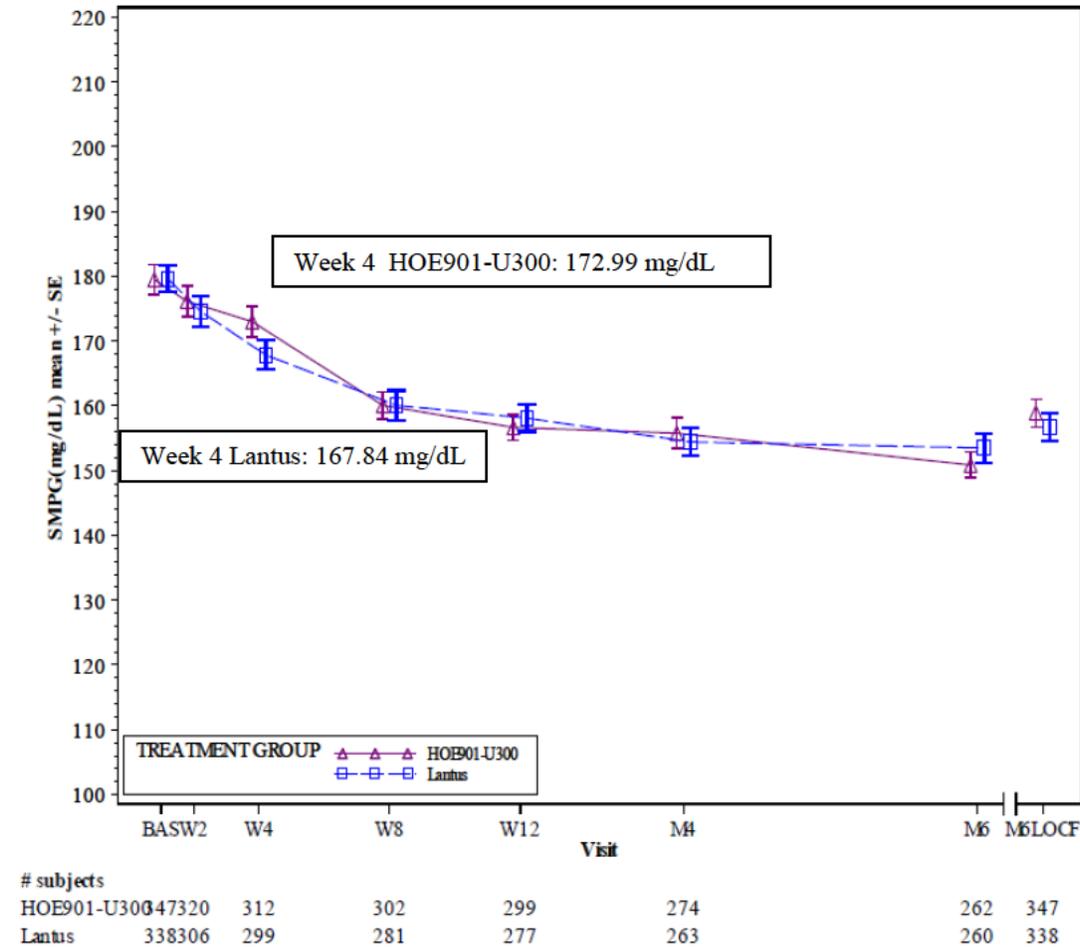
**Reviewer’s comment: Despite decrease in FPG in both groups, there was a larger adjusted decrease in the Lantus (-21.9 mg/dL) compared to HOE901-U300 (-18.5 mg/dL) group. These results, suggest that higher doses of HOE901-U300 lead to slightly less glycemic control (compared to Lantus).**

#### 6.1.4.3.3 Other endpoints - EFC11629 - T2DM

##### SMPG measures- Study EFC11629

SMPG 24-hour average plasma glucose results (from 8-point SMPG profiles), show that there was a transient increase in SMPG values in the HOE901-U300 compared to the Lantus group at Week 4. SMPG values decrease similarly between the two groups up to Week 12.

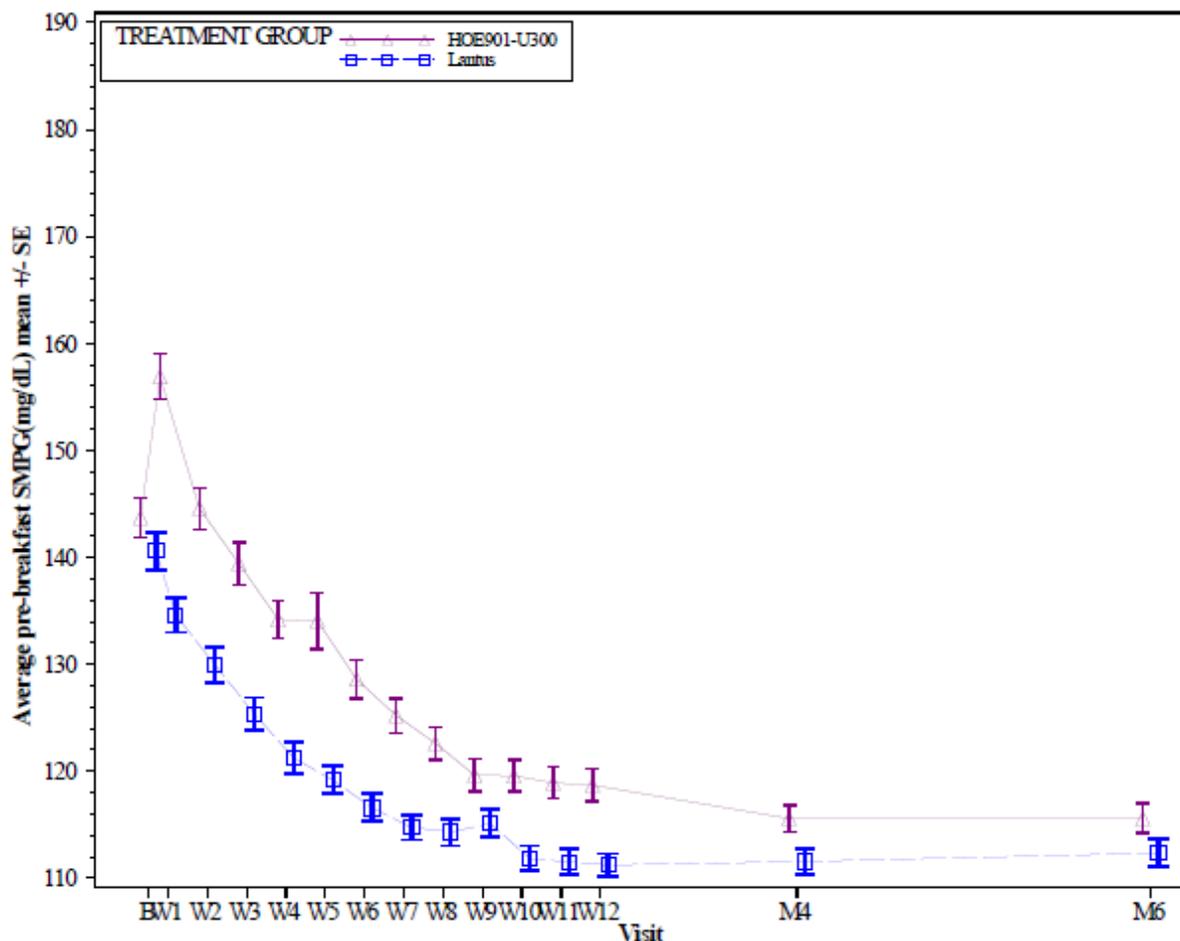
**Figure 24- EFC11629 - 24-hour average plasma glucose based on 8-point profile SMPG (mg/dL; mean ± SE) by visit (main 6-month on-treatment period; mITT population)**



Source of figure: CSR, Appendix 16.2.6.3.6.7.1; SMPG values were obtained from CSR 16.2.6.3.6.4.1

There was a peak of pre-breakfast SMPG values at 2 weeks observed (Figure 25) in the HOE901-U300 group. Overall, pre-breakfast SMPG values, in the HOE901-U300 group, remained higher than in the Lantus group during the 6-month on treatment period.

**Figure 25 – EFC11629- Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period**



Source: Sponsor response, Nov 26, 2014

**Reviewer’s comment:** Although SMPG data can be considered exploratory, both the pre-breakfast SMPG data suggest that HOE901-U300 has a decreased pharmacodynamic effect than Lantus and could be at risk of early hyperglycemia upon switching from other insulins to HOE901-U300. The higher HOE901-U300 SMPG pre-breakfast values at Week 2 are seen in other studies (EF12456 and EFC11628). Refer to 7.3.5 *Submission Specific Primary Safety Concerns* for details regarding hyperglycemia in the first week of this study.

Body Weight-Study EFC11629

The mean±SD increase in body weight from baseline to Month 6 was numerically lower in the HOE901-U300 group compared to the Lantus group: 0.08±3.45 kg vs 0.66±3.01 kg respectively.

**Reviewer’s comment:** The difference in body weight between the two groups is small and likely due to chance.

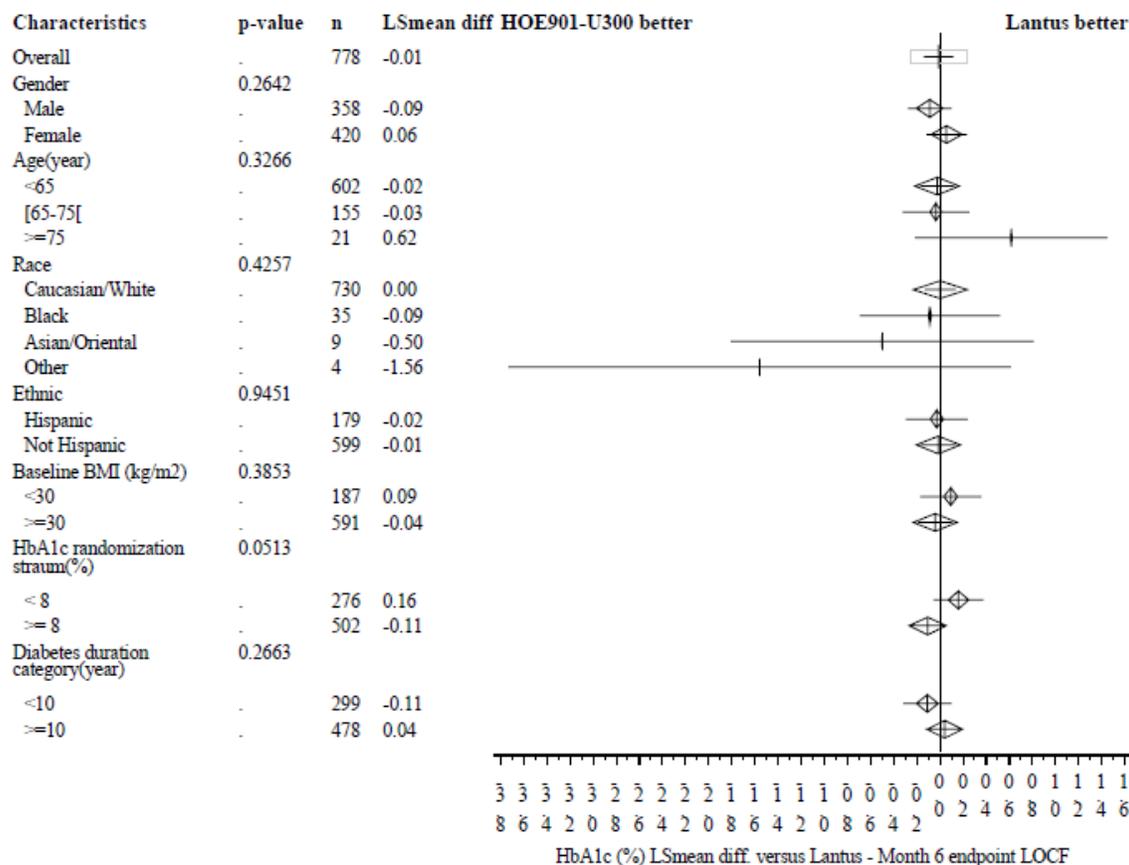
#### Rescue therapy

The percentage of patients who needed rescue therapy during the main 6-month on-treatment period was similar in both treatment groups (23 patients [5.7%] in the HOE901-U300 group and 20 patients [4.9%] in the Lantus group). The most frequent rescue therapy used was rapid-acting insulin analogs.

#### **6.1.4.3.4 Subpopulations - EFC11629- T2DM**

Overall, the treatment effect of HOE901-U300 compared to Lantus was consistent across the tested subgroups. There were no treatment effect differences across subgroups. See Figure 26, below.

**Figure 26 - Subgroup analyses on primary efficacy endpoint - Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using LOCF procedure by baseline characteristics – mITT population**



LOCF = Last observation carried forward.

BMI= body mass index.

<sup>a</sup>subgroup p-values assessing treatment-by-factor interaction come from analysis of covariance (ANCOVA) model with treatment groups (HOE901-U300 and

LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%), country, subgroup and its interaction- by-treatment group as fixed effects and baseline

HbA1c value as covariate. HbA1c randomisation strata is removed from the model when HbA1c stratum is used as baseline factor.

Note: For all patients rescued during the 6-month period, the last postbaseline HbA1c measurement before rescue and during the 6-month on-treatment period will be used as the HbA1c endpoint.

Source: Study CSR, Figure 4

#### 6.1.4.4.1 Primary efficacy endpoint - EFC12347 –T2DM insulin naive

The primary efficacy endpoint (change in HbA1c from baseline to endpoint [Month 6]) was analyzed using a Mixed-effect Model with Repeated Measures (MMRM) approach, under the missing at random framework.

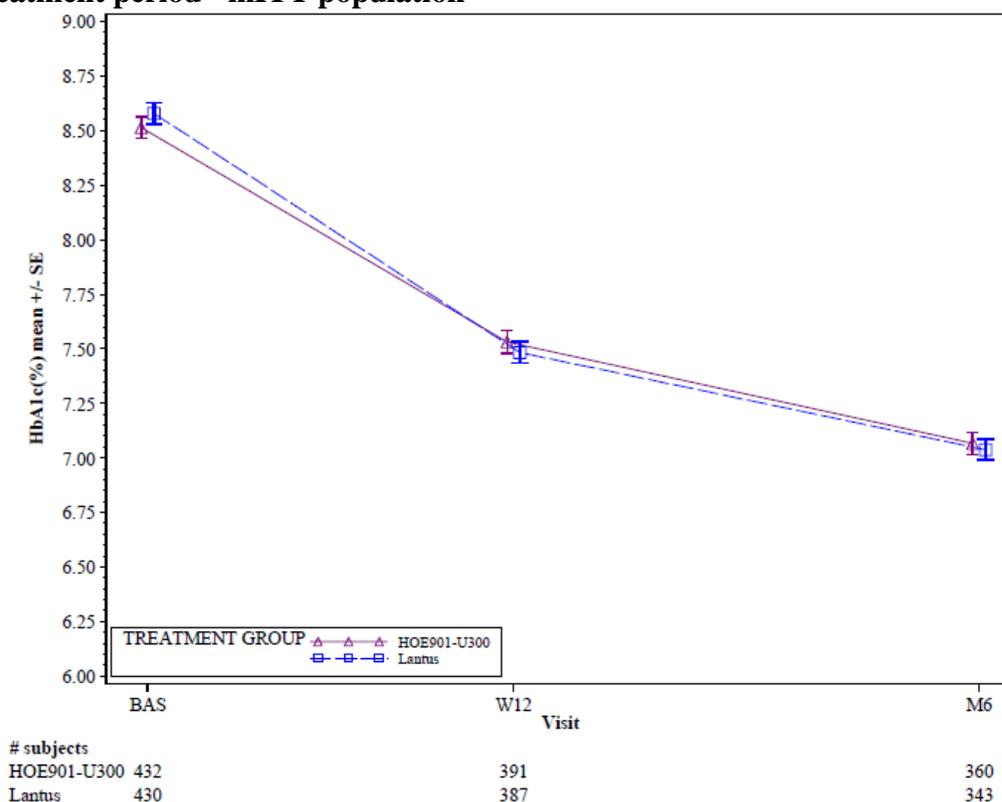
**Reviewer’s comments: Following the FDA recommendation, in August 2013**

**Advice/information correspondence with the Sponsor, the primary analysis method for**

**handling of missing data for efficacy was modified to replace LOCF method with MMRM for the primary outcome and subgroup analyses.**

In this insulin naive, T2DM trial, the 6-month change in HbA1c by HOE901-U300 met the noninferiority margin of 0.4% compared to Lantus. Refer to Figure 27 and Table 35 for details.

**Figure 27 - EFC12347 - Mean ( $\pm$ SE) HbA1c (%) by visit during the main 6-month on-treatment period - mITT population**



BAS = Baseline.  
Source: Study CSR

Figure 27 shows that mean change in HbA1c from baseline (BAS) to month 6 (M6) in both treatment groups was similar. Most of the change in HbA1c occurred in the first 12 weeks of treatment in both groups. The primary efficacy endpoint was the change from BAS (defined as Day 1 - the beginning of the randomization period), to month 6. The Sponsor's analysis showed a decrease in HbA1c in HOE901-U300 (mean $\pm$ SD) from a baseline of 8.49% $\pm$ 1.04 to 7.08 $\pm$ 0.96, a difference of -1.40% $\pm$ 1.10 from baseline. In the Lantus group, the HbA1c decreased from (mean $\pm$ SD) a baseline of 8.58% $\pm$ 1.07 to 7.05% $\pm$ 0.95, a difference of -1.53% $\pm$ 1.19 from baseline. The between drug group LS mean difference $\pm$ SE (HOE901-U300 vs Lantus) was 0.04% $\pm$ 0.067 with a 95% CI of -0.090 to 0.174. The upper bound of the 95% CI (0.174%) was below the margin of 0.4%, thus meeting the prespecified non-inferiority margin.

**Table 35 - EFC12347- Main efficacy analysis - Mean change in HbA1c (%) from baseline to endpoint (Month 6) using MMRM analysis - mITT population**

HbA1c (%)	HOE901-U300 (N=432)	Lantus (N=430)
Baseline		
Number	402	394
Mean (SD)	8.49 (1.04)	8.58 (1.07)
Median	8.30	8.40
Min : Max	6.2 : 11.3	6.7 : 11.7
Month 6 endpoint (MMRM)		
Number	365	350
Mean (SD)	7.08 (0.96)	7.05 (0.95)
Median	6.90	6.90
Min : Max	5.0 : 12.1	5.3 : 12.0
Change from baseline to Month 6 endpoint (MMRM)		
Number	365	350
Mean (SD)	-1.40 (1.10)	-1.53 (1.19)
Median	-1.30	-1.40
Min : Max	-4.8 : 3.2	-5.4 : 3.7
LS Mean (SE) <sup>a</sup>	-1.42 (0.047)	-1.46 (0.048)
95% CI	(-1.511 to -1.326)	(-1.555 to -1.367)
LS Mean difference (SE) vs. Lantus <sup>a</sup>	0.04 (0.067)	
95% CI	(-0.090 to 0.174)	

MMRM = Mixed model for repeated measurements

<sup>a</sup>MMRM model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%), randomization strata of geographical region (Non-Japan; Japan), visit (Week 12, Month 6) and visit-by-treatment groups interaction as fixed categorical effects, as well as, baseline HbA1c value and baseline HbA1c-by-visit interaction as continuous fixed covariates.

Notes: For all patients rescued during the 6-month period, only the post-baseline HbA1c measurements before rescue and during the 6-month on-treatment period are considered in the analysis.

MMRM value is either the observed value at selected visit or value retrieved according to time windows defined in the SAP.

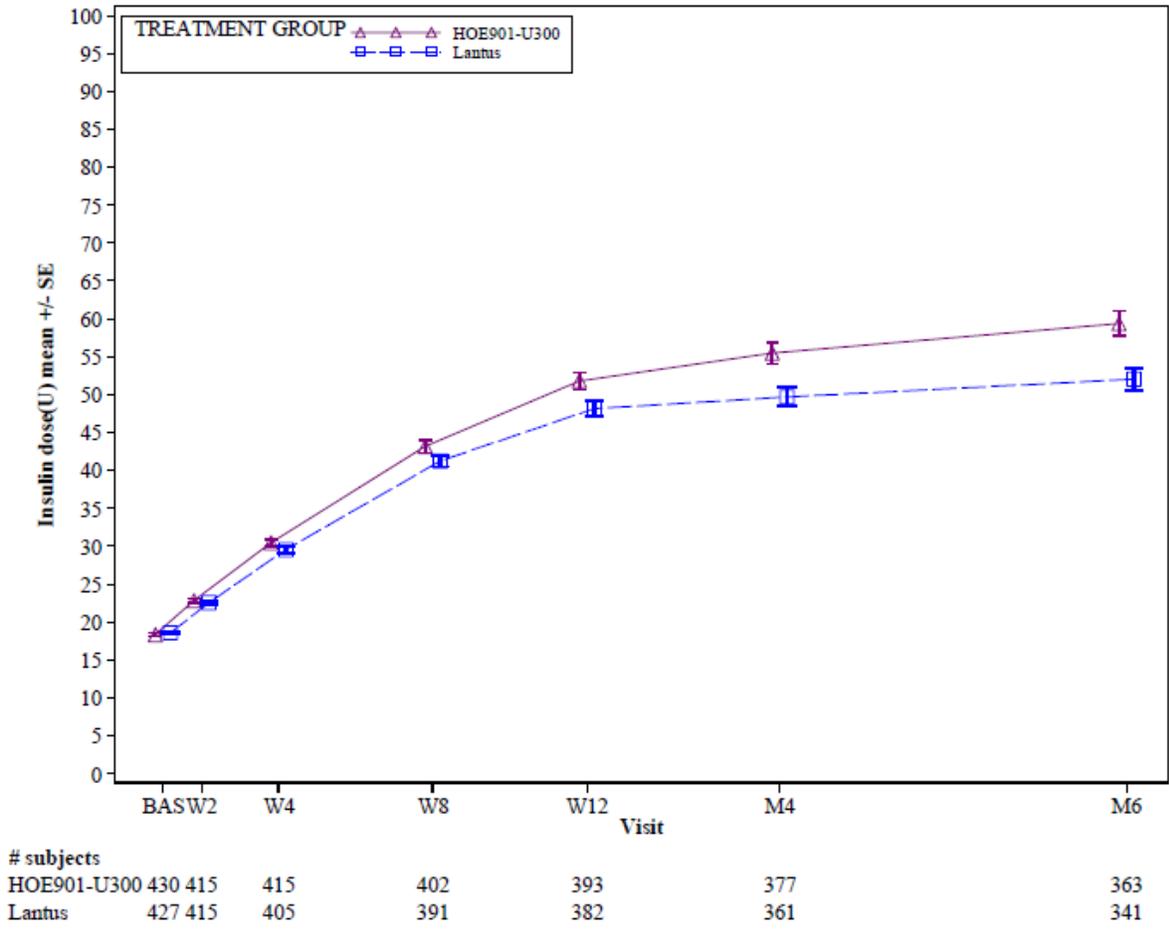
Source: Study CSR Table 14

#### EFC12347 - Mean daily insulin dosage

Refer to Table 12 for dose change details. At baseline, the average daily basal insulin starting doses were comparable in both treatment groups (HOE901-U300: 18.3 U [0.19 U/kg]; Lantus: 18.6 U [0.19 U/kg]), refer to Figure 28. Throughout the study, the basal insulin dose increased in both groups, with a greater increase in the HOE901-U300 more than the Lantus group (Month 6:

HOE901-U300: 59.4 U [0.62 U/kg] and Lantus: 52 U [0.53 U/kg]). At month 6, the HOE901-U300 group required 7.4 more units of insulin than the Lantus group.

**Figure 28 - EFC12347 - Mean (+/- SE) in average daily insulin dose (U) by visit during the main 6-month on-treatment period - mITT population**

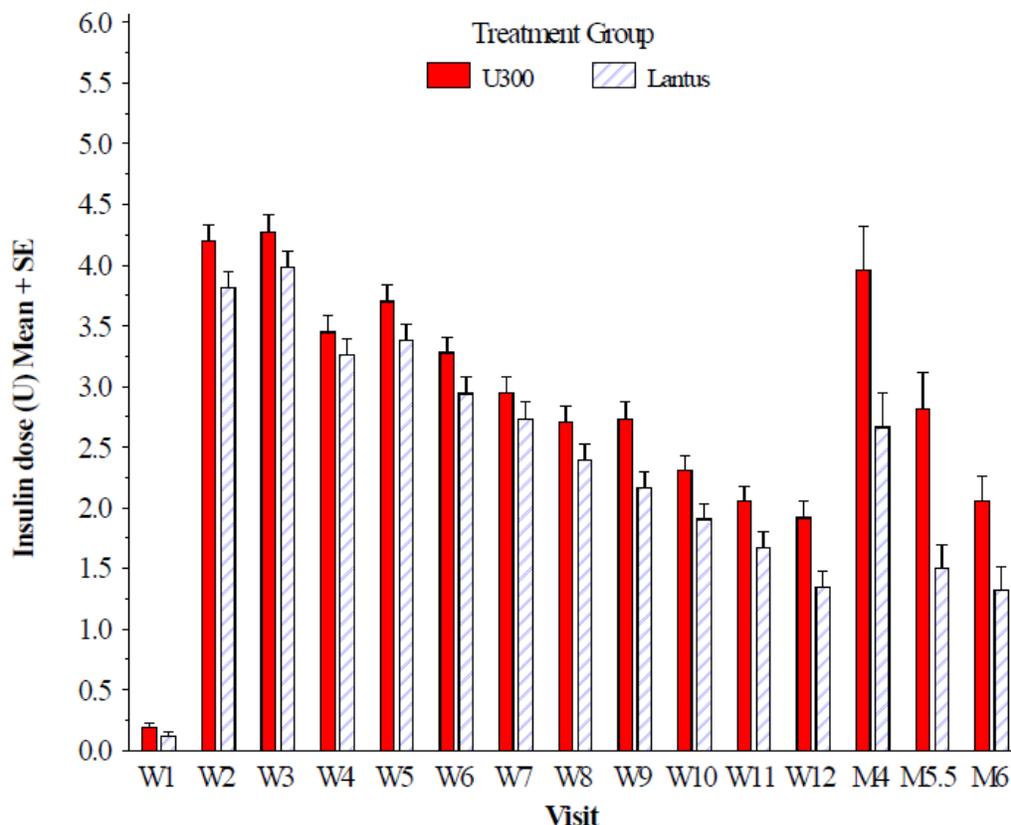


Source Study CSR, Figure 13

The Sponsor's analysis of titration (by visit) shows that HOE901-U300 was titrated at higher insulin doses than Lantus at every visit (see Figure 29).

Refer to Table 7 for details regarding minimum titration allowable by the pen devices used in this study.

**Figure 29 – EFC12347 - Mean (SE) change in daily average basal insulin dose (U) between consecutive visits of the main 6-month on-treatment period in mITT population**



Note: For all patients rescued during the 6-month on-treatment period, only the post-baseline insulin doses before rescue and during the 6-month on-treatment period are considered in the analysis.

Note: for each visit the mean change from previous visit is displayed (examples : “W1” represents the change in insulin Dose between “Week1” and “Baseline” visits; “M4” represents the change in insulin Dose between “Month 4” and “Week 12” visits)

Source: Sponsor’s analysis, per information request

**Reviewer’s comments:**

**Despite similar starting doses of insulin in both treatment groups (0.19 U/kg), HOE901-U300 required higher (0.62 U/kg) dosage compared to Lantus (0.53 U/kg), to achieve a slightly worse glycaemic control (HOE901-U300:-1.42% decrease of HbA1c vs. Lantus: -1.46% decrease of HbA1c). This data in insulin naive patients also suggests that HOE901-U300 may have a lesser pharmacodynamic effect than Lantus.**

Sensitivity Analyses of the Primary Endpoint

The four sensitivity analyses (analysis to assess the impact of rescue medication based on all scheduled HbA1c measures in the mean treatment period, analysis for primary efficacy endpoint adjusted by days of concomitant rescue medications, analysis performed using LOCF values as HbA1c endpoint, analysis of Month 6 completer population to assess the impact of missing data on mean change in HbA1c) performed by the sponsor to assess the impact of missing data on

mean change in HbA1c from baseline to Month 6 supported the conclusion of the primary analysis.

Patients taking rescue therapy were excluded from the sensitivity analysis on the primary efficacy endpoint using the completers population. This number was low, with 7 patients 1.6% in the HOE901-U300 and 15 patients, 3.5% in the Lantus group.

#### 6.1.4.4.2 Secondary endpoints - EFC12347- T2DM

The Sponsor followed the hierarchical testing procedure (specified in SAP, see 5.3 Discussion of Individual Studies/Clinical Trials for details), to evaluate for superiority (adjusting for multiplicity), of HOE901-U300 for the main secondary endpoints. (b) (4)

(b) (4)

(b) (4)

**Table 36 - EFC12347- First main secondary efficacy endpoint - Number (%) of patients with at least one nocturnal hypoglycemia [00:00 to 05:59] occurring between start of Week 9 and Month 6, indicated as severe and/or confirmed by plasma glucose  $\leq$  3.9 mmol/l (70 mg/dL) – mITT**

(b) (4)



Table 37 for secondary endpoints that further characterize the glycemic control of both HOE901-U300 vs. Lantus

**Table 37 - EFC12347 - Selected secondary efficacy endpoints- Number (%) of patients – mITT population**

(b) (4)

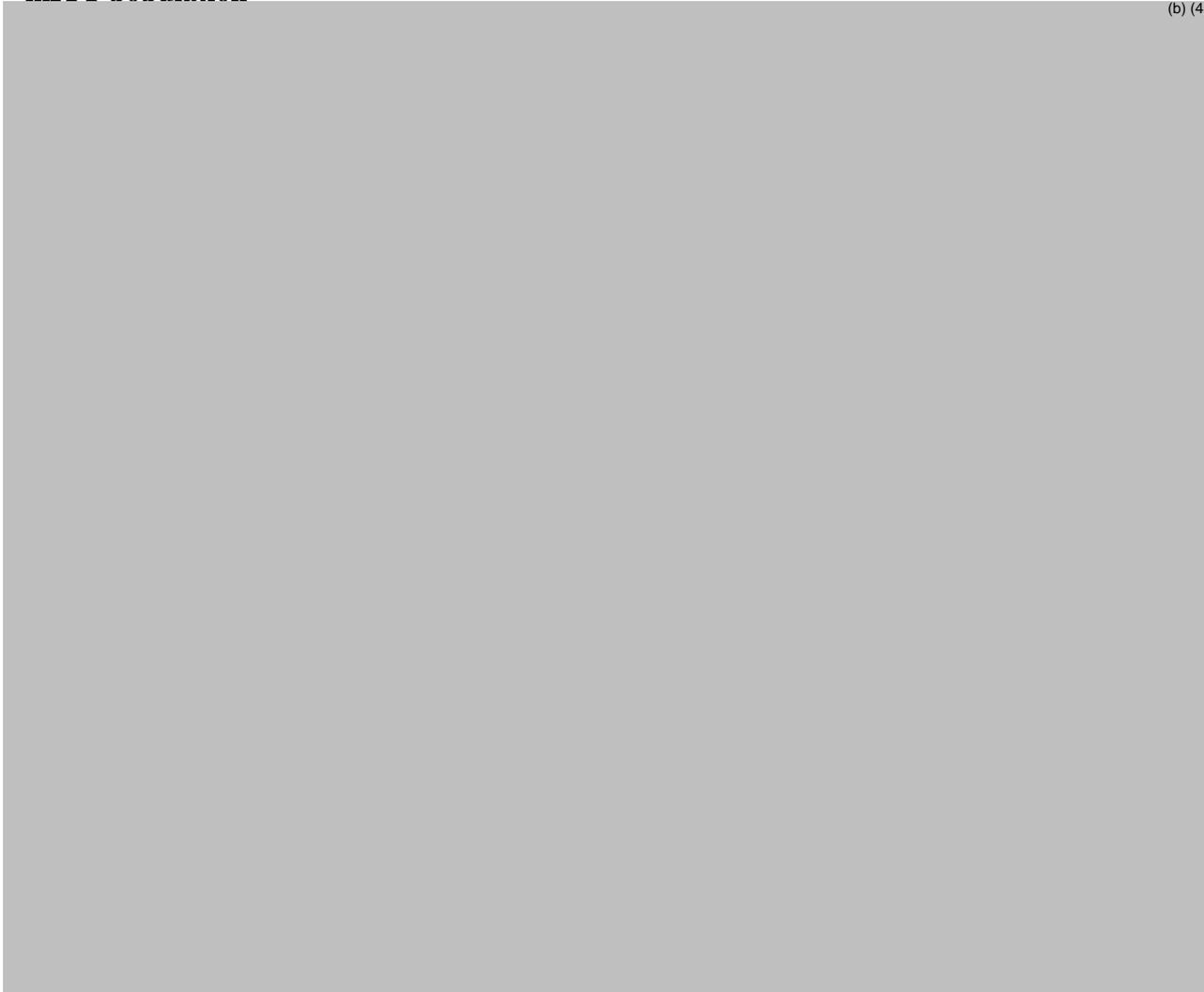


Table 38 shows the change in fasting plasma glucose from baseline to Month 6. In both treatment groups, FPG declined mostly in the first 12 weeks of therapy.

**Table 38 - EFC12347 - Other secondary efficacy endpoint - Mean change in FPG (mg/dL) from baseline to endpoint (Month 6) using MMRM analysis - mITT population**

FPG (mg/dL)	HOE901-U300 (N=432)	Lantus (N=430)
<b>Baseline</b>		
Number	398	387
Mean (SD)	178.89 (51.46)	184.00 (52.19)
Median	173.50	177.00
Min : Max	54.0 : 416.1	65.0 : 454.0
<b>Month 6 endpoint (MMRM)</b>		
Number	359	344
Mean (SD)	120.19 (38.85)	113.55 (32.75)
Median	113.00	108.09
Min : Max	57.0 : 382.0	59.0 : 243.0
<b>Change from baseline to Month 6 endpoint (MMRM)</b>		
Number	359	344
Mean (SD)	-59.22 (58.05)	-70.35 (55.45)
Median	-59.00	-67.33
Min : Max	-290.0 : 200.0	-339.0 : 84.7
LS Mean (SE) <sup>a</sup>	-61.51 (1.850)	-68.50 (1.887)
95% CI	(-65.146 to -57.882)	(-72.208 to -64.799)
LS Mean difference (SE) vs. Lantus <sup>a</sup>	6.99 (2.643)	
95% CI	(1.800 to 12.178)	

FPG=Fasting Plasma Glucose

MMRM = Mixed model for repeated measurements

<sup>a</sup>MMRM model with treatment groups (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%), randomization strata of geographical region (Non-Japan; Japan), visit (Week 12, Month 6) and visit-by-treatment groups interaction as fixed categorical effects, as well as, baseline FPG value and baseline FPG-by-visit interaction as continuous fixed covariates.

Notes: For all patients rescued during the 6-month period, only the post-baseline FPG measurements before rescue and during the 6-month on-treatment period are considered in the analysis.

MMRM value is either the observed value at selected visit or value retrieved according to time windows defined in the SAP.

Source: Study CSR, Table 22

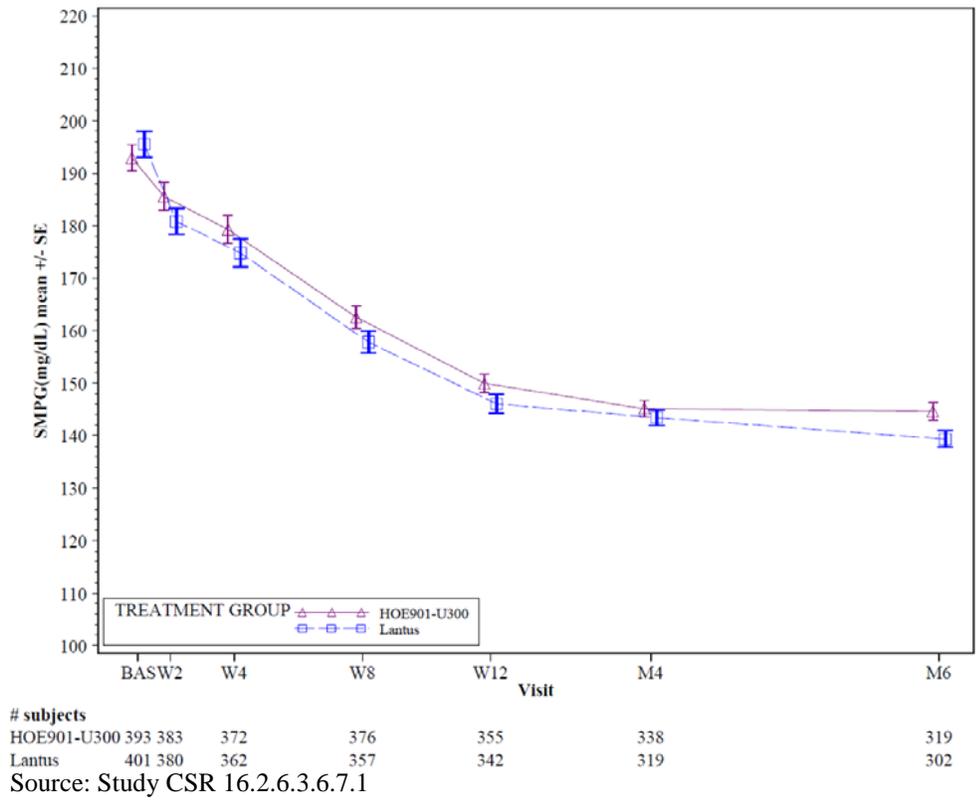
**Reviewer's comments: Although HOE901-U300 and Lantus had decreases in FPG throughout the 6-month treatment period, the adjusted between group, difference (+6.99 mg/dL) showed that despite higher dosages of HOE901-U300, achieved fasting plasma glucose was higher than that of Lantus (95% CI 1.8 to 12.2).**

**6.1.4.4.3 Other endpoints - EFC12347 – T2DM**

**Study EFC12347 – SMPG measures**

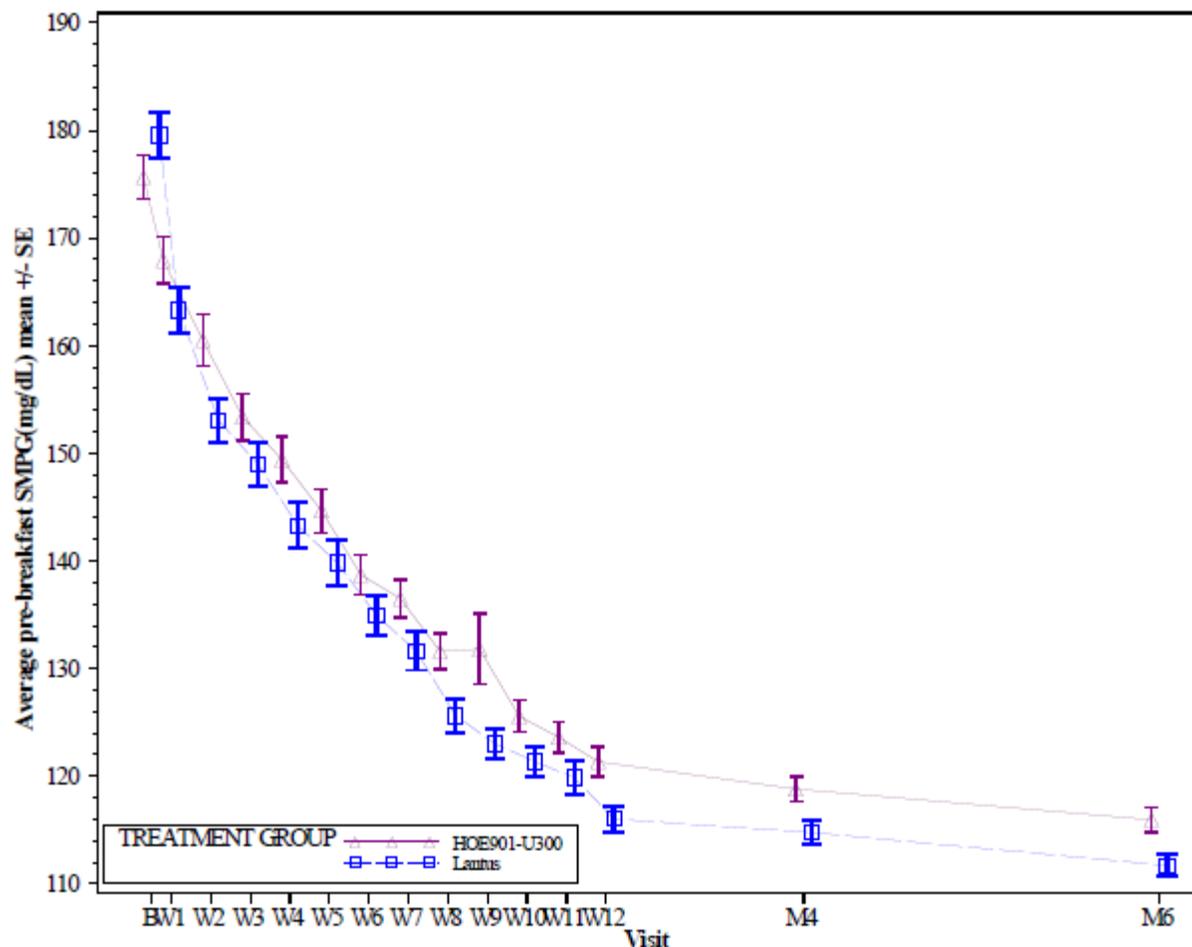
SMPG 24-hour average plasma glucose results (from 8-point SMPG profiles), show that there was higher SMPG values in the HOE901-U300 compared to the Lantus group after Week 2 until the end of the study.

**Figure 30 – EFC12347- Mean (+/- SE) in 24-hour average 8-point SMPG profiles (mg/dL) by visit (main 6-month on-treatment period; mITT population)**



Similar findings were seen in the average pre-breakfast SMPG values during the 6-month on treatment period.

**Figure 31 – EFC12347 – Mean (+/- SE) in average pre-breakfast SMPG (mg/dL) by visit during the main 6-month on-treatment period**



Source: Sponsor response, Nov 26, 2014

**Reviewer's comment:** Unlike the other studies which showed higher SMPG (8-point and pre-breakfast) readings in the HOE901-U300 group earlier in the study, (i.e. a peak at 2 or 4 weeks), compared to the Lantus group, this study does not show a peak in SMPG glucose values in the HOE901-U300. This finding is likely due to the study design in that the patients in this trial were insulin naïve and were not being changed from a commercial basal insulin product.

#### EFC12347 - Body Weight

The mean±SD change in body weight from baseline to Month 6 was numerically lower in the HOE901-U300 group compared to the Lantus group: 0.50±3.70 kg vs 0.71±3.61 kg respectively.

#### **Reviewer's comment:**

**The difference in body weight was less than 1 kg in both groups. Despite higher insulin doses used in the HOE901-U300 group, there was a slightly lower weight gain in this group**

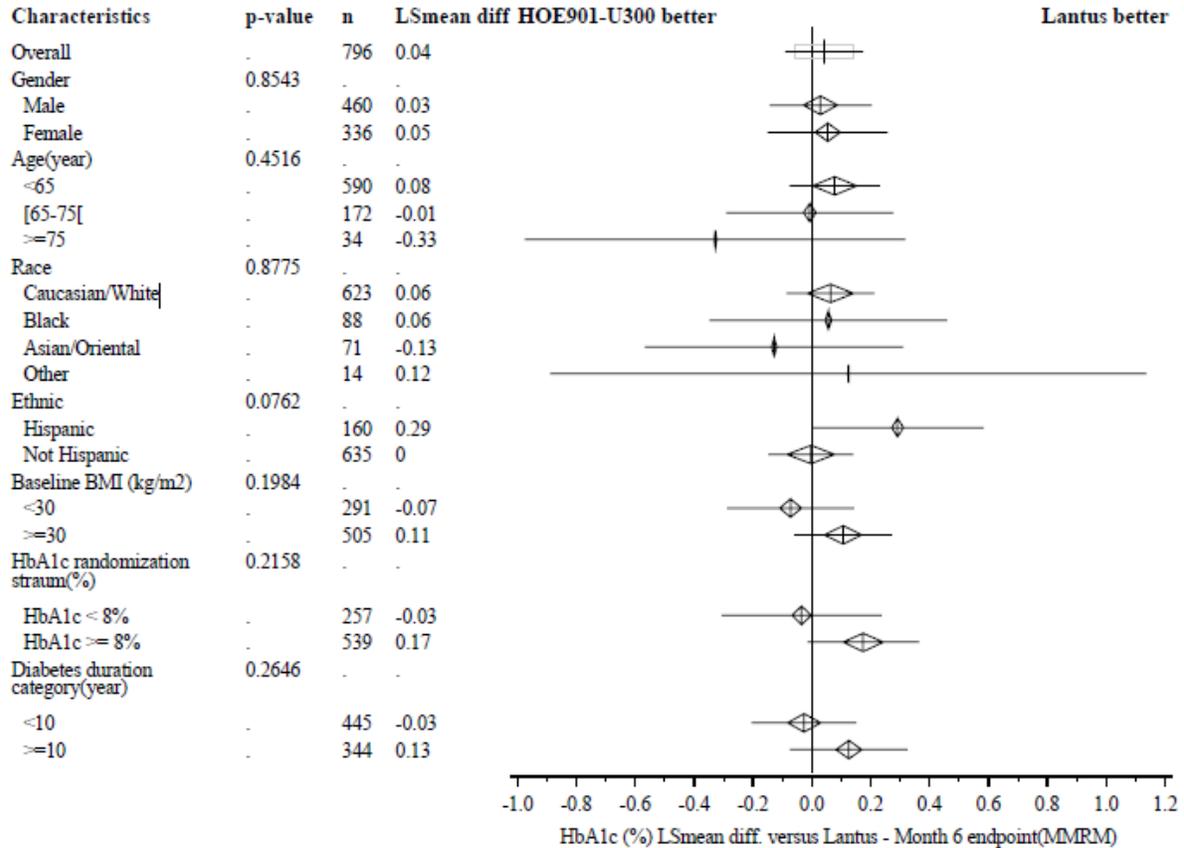
**compared to the Lantus group. A reason for the differences in weight gain between the two groups is not clear.**

The percentage of patients in whom rescue therapy was initiated during the main 6-month on-treatment period was lower in the HOE901-U300 group (7 patients [1.6%]) than in the Lantus group (15 patients [3.5%]). Rescue treatment was initiated mostly after 90 days of study treatment.

#### **6.1.4.4 Subpopulations - EFC12347 - T2DM**

Overall, the treatment effect of HOE901-U300 versus Lantus was consistent across tested subgroups. No treatment by subgroup interaction was observed. See Figure 32 below for details.

**Figure 32 - Subgroup analyses on primary efficacy endpoint - Forest plot of mean change in HbA1c (%) from baseline to endpoint (Month 6) using MMRM analysis characteristics - mITT population**



MMRM = Mixed model for repeated measurements. BMI= body mass index.

Subgroup p-values assessing treatment group-by-subgroup factor interaction come from analysis of MMRM model with treatment group (HOE901-U300 and LANTUS), randomization strata of screening HbA1c (<8.0, ≥8.0%), subgroup factor, visit (Week 12, Month 6), visit-by-treatment group interaction, subgroup factor-by-treatment group interaction, subgroup factor-by-visit interaction and subgroup factor-by-treatment group-by-visit interaction as fixed categorical effects, as well as, baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates.

Notes: When the subgroup considered is equal to the randomization stratum of screening HbA1c (<8.0, ≥8.0%), the baseline HbA1c value, as well as, the baseline HbA1c-by-visit interaction are removed from the model.

For all patients rescued during the 6-month period, only the post-baseline HbA1c measurements before rescue and during the 6-month on-treatment period are considered in the analysis.

Source: Study CSR, Figure 4

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing issues are discussed throughout this review.

## 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Duration of action is discussed in section 4.4.2 Pharmacodynamics.

### 6.1.10 Additional Efficacy Issues/Analyses

None.

## 7 Review of Safety

### Safety Summary

The major safety findings of this review are summarized in this section.

Deaths: During the pre-agreed upon main-6 month treatment period (up to dossier cut off 29 October 2013), as well as the 120-Day Safety Update report, there was no imbalance in the incidence of deaths between HOE901-U300 and Lantus. I concluded that none of the deaths were likely to be caused by IMP.

SAEs: Among the T1DM patients, there was no pattern of a single type of SAE that occurred with significantly greater frequency among HOE901-U300- treated patients than among Lantus-treated patients. Among the T2DM subjects, there was a higher rate of cerebrovascular disorders seen in the Lantus group vs. HOE901-U300.

Premature discontinuation due to adverse events was also balanced between the two groups.

Submission specific safety concerns reviewed included hypoglycemia, cardiovascular events, neoplasms, injection site reactions, and immunogenicity. Overall, the rates of hypoglycemia were comparable between HOE901-U300 and Lantus and should be interpreted in context of glycemic control. Analysis of cardiovascular safety did not suggest a concerning signal for cardiovascular risk, although, because the product is an insulin, the development program was not designed to rigorously assess cardiovascular risk. No safety signal for any type of malignancy neoplasm was seen in the HOE901-U300 development program. In general, insulin antibodies did not differ in HOE901-U300 compared to Lantus (although as expected their presence was higher in the T1DM compared to the T2DM population). Regardless of antibody presence or level, there was no apparent clinical impact of these antibodies on glycemic control.

Common adverse events: Nasopharyngitis and upper respiratory infections were the most common adverse events among HOE901-U300 and Lantus treated patients in the phase 3 controlled clinical trials. The incidence of these events was balanced between groups for the most part.

## 7.1 Methods

The reviewer performed the safety review by evaluating the pooled T1DM and T2DM populations separately, except for rare events, (such as deaths), where the analysis was combined. Within each population (T1DM and T2DM), I evaluated studies separately when indicated (for example due to different study duration). I reviewed non-pooled studies (such as substudies) when pertinent. I focused on any safety signals found in the pivotal trials by in-depth review of the submitted study reports, narratives, and datasets. All of the submitted narratives for deaths and nonfatal SAEs were reviewed. The 120-Day Safety Update Report was reviewed and is mentioned throughout the safety review.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The data sources used in the safety assessment were adequate. In general, the Sponsor's methods were appropriate for the safety evaluation.

The safety population was defined by the Sponsor as all randomized patients who were exposed to at least one dose of IMP. All safety data is presented according to the actual treatment the subject received. The safety assessments and analyses include data available as of the dossier cutoff date, 29 October 2013.

Data from the initial 6 months of the 4 pivotal Phase 3 studies (EFC12456, EFC11628, EFC11629, and EFC12347) as well as from the Phase 2 study (PDY12777) completed their treatment period at the time of the dossier cut-off date (29 October 2013) and are included in the pooled Phase 2/3 safety database for this NDA.

Data **not included** in the Phase 2/3 safety database:

- data from substudy EFC11628 and substudy EFC11629
- data from 6 clinical Phase 3 studies/safety extensions that were ongoing at the data cut-off date

The reason why these extension periods of Phase 3 studies are not included in the safety database is prior agreement by the Agency that 6-month of treatment data at the time of NDA submission was acceptable.

The 120-Day Safety Update Report, as agreed with FDA during the Pre-NDA meeting, includes safety information from the 4 pivotal Phase 3 studies (EFC12456, EFC11628, EFC11629 and EFC12347) and 2 Japanese Phase 3 studies (EFC12449 and EFC12512). The safety assessments and analyses included in the 120-Day Safety Update Report include data as of the cut-off date April 21, 2014. At the time of this cut-off date, two of the pivotal Phase 3 studies (EFC11628 and EFC11629) completed the 12-month on-treatment period (in addition to the 4-week post-treatment follow-up period) and both Japanese Phase 3 studies completed the main 6-month on-treatment period. Ongoing studies at the time of the 120-Day Safety Update Report included EFC12347 and EFC12456.

Section 7.5.1 Dose Dependency for Adverse Events in this review focuses on the safety data of converting from doses of HOE901-U300 to other insulins.

See Table 39 for a complete listing of completed and ongoing trials. Refer to section 5.1 Tables of Studies/Clinical Trials for a description of each trial.

**Table 39 - Overview of Clinical Safety Data**

Completed controlled safety/ efficacy trials 6-month on treatment period.	T1DM	<b>EFC12456, PDY12777<sup>a</sup></b>
	T2DM	<b>EFC11628, EFC11629, EFC12347</b>
Completed clinical pharmacology, Phase1 trials	Healthy volunteers	PKD10086
	T1DM	PKD11627, PKD12270, TDR11626, PKD13560, PDY12335
Completed 3-month substudies NOT included in the integrated safety database	T2DM	EFC11628 substudy, EFC11629 substudy
Ongoing trials (6-month safety extension periods). Results NOT included in the integrated safety database	T1DM	<b>EFC12456, EFC12449<sup>b</sup>, EFC12512<sup>c</sup></b>
	T2DM	<b>EFC11628, EFC11629 and EFC12347</b>
Source, ISS Items in <b>bold</b> font refer to pivotal Phase 3 studies. <sup>a</sup> Trial was a 16 week, exploratory trial <sup>b</sup> 6-month open label trial in Japan in patients with T1DM with a 6-month extension period <sup>c</sup> 6-month open label trial in Japan in patients with T2DM with a 6-month extension period		

### 7.1.2 Categorization of Adverse Events

This section describes the terminology and taxonomy used to characterize adverse events and the periods of observation during which these terms were applied.

Per the Sponsor, the term “adverse event” (AE) was defined as any untoward medical occurrence in a clinical investigation in which a patient is administered a pharmaceutical product. All AE data were collected by spontaneous reporting from the time the patient signed the informed consent form to the end of each study. Adverse events were reported using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0. According to this dictionary, each AE is coded to: a lowest level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT) and associated primary System Organ Class (SOC).

**Treatment Emergent Adverse Events (TEAEs)** were defined as AEs that developed, worsened, or became serious during the main on-treatment period (see below for definitions of the periods of observation). If the treatment status for an AE was unclear due to missing or incomplete onset date, it was always considered as treatment-emergent, unless otherwise shown by data.

**Serious Adverse Events (SAEs)** were defined according to the internationally agreed criteria (International Conference on Harmonization [ICH] E2A), in which a serious adverse event is any untoward medical occurrence that at any dose results in death, or is life threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe. The event requires any of the three following criteria: inpatient hospitalization, or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect<sup>1</sup>.

The term “**severe**”<sup>1</sup> is used to describe the intensity (severity) of a specific event.

The Sponsor described the periods of observation as follows:

- **pretreatment phase** - the time between the signature of the informed consent and the start of the first IMP administration
- **on-treatment phase** - the time from the first randomized IMP administration of a period until 3 days after the last dose of IMP of each period
- **post-treatment phase** - the time after the on-treatment phase until either the (first) administration of IMP in the next period or the end of study

**Reviewer’s comment: The terminology used by the Sponsor to describe the periods of observation is confusing. For example in the on-treatment phase and the post-treatment phase, patients receive IMP, but the terminology suggests that treatment has stopped during the post-treatment phase. The analysis provided by the Sponsor is only of the on-treatment phase (due to prior agreement with Agency). Essentially, the ‘on-treatment phase’ describes the 6 month efficacy portion of the trial, and the ‘post-treatment phase’ describes the 6 month controlled safety extension.**

The safety of study treatment was evaluated on the rate, type, severity, and causality of adverse events (AE).

The rate and type of the following events were presented by the Sponsor and were reviewed:

- deaths
- serious adverse events (SAEs)
- adverse events leading to dropout
- systematically evaluated AEs
  - injection site
  - hypersensitivity reactions
  - cancers
  - cardiovascular events
  - hepatic events
  - symptomatic overdose (accidental or intentional) with IMP/non-IMP
- AEs in key demographic and baseline subgroups
- AEs related to pregnancy

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<sup>1</sup> International Conference on Harmonization [ICH] E2A

- changes from baseline in laboratory variables, vital signs, body weight, EKG
- hypoglycemia

When describing patient narratives in this review, a patient identifier number will be used. The first six digits of each patient identifier specify the trial in which the patient was enrolled.

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

Incidence of adverse events was evaluated from pooled controlled Phase 2 and Phase 3 study data. For Phase 2/3, data was pooled as follows, for most AE except for hypoglycemia (which is discussed below):

- T1DM pool: main 6-month on-treatment period for Study EFC12456 and 16-week on-treatment period of Study PDY12777
- T2DM pool: main 6-month on-treatment period for studies EFC11628, EFC11629, and EFC12347
- Overall pool: For the complete overview of safety data in the exposed Phase 2/3

Hypoglycemia was analyzed by trial. Hypoglycemia assessments in the T1DM, T2DM, or overall pools were not provided due to the following reasons:

- T1DM pool: the design (16-week duration, AM and PM injection with switch after 8 weeks) of study PDY12777 might cause an increased number of episodes of hypoglycemia.
- T2DM pool: different antidiabetic treatment regimens were used in the studies. Studies EFC11629 and EFC12347 were performed in patients receiving basal insulin and non-insulin AHA and therefore these data are presented in a separate pool (study pool on basal insulin and non-insulin AHA).
- T1DM and T2DM were not pooled together due to the different pathology

Non-pooled trials included data from the 3-month substudy EFC11628 and substudy EFC11629. These substudies were not pooled since the studies examined changes in efficacy and safety in HOE901-U300 only (without a comparator).

**Reviewer's comments: The Sponsor's pooling strategy is consistent with strategies commonly used in the drug development program and is acceptable.**

## **7.2 Adequacy of Safety Assessments**

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

The population exposed to IMP in clinical trials should reflect the larger population for which the drug is targeted. In this section, the reviewer discusses the overall population, the population split by diabetes type (T1DM and T2DM), and the population split by demographic characteristics.

Overall exposure in Phase 2/3 (T1DM and T2DM pools)

The number of patients exposed to HOE901-U300 adheres to both: pre-submission agreements between the Sponsor and the FDA and adheres to the FDA's published Guidance<sup>1</sup>. In the Phase 2/3 program, 3,096 patients were exposed to study treatment (1546 to HOE901-U300 and 1550 to Lantus) and were included in the safety analyses. Table 40 shows the number of subjects exposed by defined duration, separated by type of diabetes as of the cut-off date (29 October 2013).

#### Exposure in the Phase 2/3- T1DM population

The different durations of the two T1DM studies (EFC12456 - 6 months; PDY12777 - 16 weeks), lessened the overall exposure in this population compared to the T2DM population (discussed below). Also, there were three pivotal studies in the T2DM population.

Patients with T1DM receiving either treatment (HOE901-U300 or Lantus) were exposed to similar durations of treatment. There was a 133 patient-year total exposure in the HOE901-U300 versus 135 patient year total exposure in the Lantus groups. The median duration of exposure was identical for the 2 treatment groups (183.0 days). Over three-quarters of patients in the safety population were exposed to study treatment for more than 25 weeks (76% in the HOE901-U300 and 77.9% in the Lantus group). The majority of patients were exposed for >26 weeks (162 patients [53.3%] and 180 patients [59.4%], respectively). Refer to Table 40 for details.

Patients with T1DM in the **United States** had similar patient-year exposure (86 in the HOE901-U300 and 81.9 in the Lantus group). The reviewer selected subgroups within the T1DM study pool, which could represent the United States population (such as exposure by race and exposure by age). The analysis of these subgroups is not shown, since the exposure between HOE901-U300 and Lantus was similar. However, it is worth noting that certain subgroups had less exposure, irrespective of drug assignment. These groups included:

1. Patients with age  $\geq 65$  to  $< 75$  (cumulative exposure by patient years:  $\sim 9$ , in either treatment group)
2. Patients with age  $\geq 75$  (cumulative exposure by patient years:  $\sim 2.5$ , in either treatment group)
3. Black patients (cumulative exposure by patient years:  $\sim 5$ , in either treatment group) vs. Caucasians who had a cumulative exposure by patient years of  $\sim 110$ 's in either treatment group

#### Exposure in the Phase 3- T2DM population

Since the main-on treatment duration for all T2DM was the same (6 months), all studies had similar exposure. The cumulative duration of treatment exposure in the T2DM population was 586.4 patient years in the HOE901-U300 and 584 patient-years in the Lantus group. The median duration of exposure was identical for the 2 treatment groups (183.0 days). Over 85% of patients in the safety population were exposed to study treatment for more than 25 weeks (88.7% in the HOE901-U300 group and 87.2% of patients in the Lantus group). The majority were exposed

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<sup>1</sup> Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, February 2008

for >26 weeks (791 patients [63.8%] for HOE901-U300 and 802 patients [64.7%] for Lantus). Refer to Table 40 for details.

Patients with T2DM in the United States had similar patient-year exposure (277 in the HOE901-U300 and 295.4 in the Lantus group). Similarly, to the analysis of T1DM, the reviewer selected subgroups within the T1DM study pool, which could represent the United States population (such as exposure by race and exposure by age). The analysis of these subgroups is not shown, since the exposure between HOE901-U300 and Lantus was similar. However, it is worth noting that certain subgroups had decreased exposure, irrespective of drug assignment. These groups included:

1. Patients with  $\text{age} \geq 75$  (cumulative exposure by patient years: 18 in HOE901-U300 vs. 21 in Lantus)
2. Black patients (cumulative exposure by patient years: ~42, in either treatment group) vs. Caucasians who had a cumulative exposure by patient years of ~510's in either treatment group.

**Table 40 - Exposure to investigational product during the main on treatment period: T1DM and T2DM study pools - Safety population**

	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Cumulative exposure to treatment (patient-years)	133.0	135.0	586.4	584.0
Duration of treatment (days)				
Number	304	303	1240	1240
Mean (SD)	159.8 (48.0)	162.7 (46.0)	172.7 (36.5)	172.0 (37.6)
Median	183.0	183.0	183.0	183.0
Min : Max	1 : 218	1 : 260	1 : 209	1 : 228
Duration of treatment by category [n(%)]				
up to 2 weeks	6 (2.0%)	8 (2.6%)	19 (1.5%)	21 (1.7%)
>2 to 4 weeks	9 (3.0%)	4 (1.3%)	12 (1.0%)	17 (1.4%)
>4 to 8 weeks	6 (2.0%)	8 (2.6%)	25 (2.0%)	21 (1.7%)
>8 to 12 weeks	8 (2.6%)	5 (1.7%)	20 (1.6%)	19 (1.5%)
>12 to 17 weeks	39 (12.8%)	34 (11.2%)	14 (1.1%)	17 (1.4%)
>17 to 26 weeks	74 (24.3%)	64 (21.1%)	359 (29.0%)	343 (27.7%)
>26 weeks	162 (53.3%)	180 (59.4%)	791 (63.8%)	802 (64.7%)
Cumulative duration treatment by category [n(%)]				
≥1 days	304 (100%)	303 (100%)	1240 (100%)	1240 (100%)
>2 weeks	298 (98.0%)	295 (97.4%)	1221 (98.5%)	1219 (98.3%)
>4 weeks	289 (95.1%)	291 (96.0%)	1209 (97.5%)	1202 (96.9%)
>8 weeks	283 (93.1%)	283 (93.4%)	1184 (95.5%)	1181 (95.2%)
>12 weeks	275 (90.5%)	278 (91.7%)	1164 (93.9%)	1162 (93.7%)
>17 weeks	236 (77.6%)	244 (80.5%)	1150 (92.7%)	1145 (92.3%)
>25 weeks	231 (76.0%)	236 (77.9%)	1100 (88.7%)	1081 (87.2%)
>26 weeks	162 (53.3%)	180 (59.4%)	791 (63.8%)	802 (64.7%)

T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Note: Patients are considered in the treatment group they actually received

Source: ISS, Table 24

**Reviewer's comments: The As per FDA Guidance<sup>1</sup> the Sponsor met the requirement of total exposure of at least 1,500 subjects (300 to 600 for 6 months, 100 for 1 year) for the safety**

<sup>1</sup> Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, February 2008

**assessment of chronically administered drugs developed for the treatment of non-life-threatening conditions.**

Demographics of safety population

Refer to Section 6 Review of Efficacy for comments regarding demographics in terms of the adequacy of randomization between HOE901-U300 and Lantus within each of the pivotal clinical trials.

Table 41 shows the demographic and baseline characteristics of patients from the safety Phase 2/3, T1DM and T2DM pools.

T1DM patients were younger, with mean age in the 40's versus T2DM patients with mean age near 60 years of age. This difference in mean age could result because more than a fifth of the T2DM patients were between ages 65-75, vs. only 7% in the T1DM population. Patients with T2DM had a higher baseline weight than those with T1DM.

In both diabetes groups, more than 50% of participants were males. There were also over 80% of Caucasian/White participants with a smaller representation of other races. Overall, more than half of the participants in the T1DM and T2DM groups were from North America. In addition, more than half of participants had an HbA1c at baseline  $\geq 8\%$ .

**Table 41 - Demographics and baseline characteristics: T1DM and T2DM study pools - safety population.**

	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Number	304	304	1242	1246
Mean (SD)	46.3 (14.0)	47.7 (13.5)	58.7 (9.2)	58.5 (9.5)
Median	47.0	49.0	60.0	59.0
Min : Max	19 : 80	18 : 86	24 : 87	27 : 86
Age Group (years) [n (%)]				
<65	274 (90.1%)	277 (91.1%)	915 (73.7%)	914 (73.4%)
[65-75[	24 (7.9%)	21 (6.9%)	290 (23.3%)	284 (22.8%)
$\geq 75$	6 (2.0%)	6 (2.0%)	37 (3.0%)	48 (3.9%)
Gender [n (%)]				
Male	166 (54.6%)	179 (58.9%)	654 (52.7%)	647 (51.9%)
Female	138 (45.4%)	125 (41.1%)	588 (47.3%)	599 (48.1%)
Race [n (%)]				
Caucasian/White	262 (86.2%)	264 (86.8%)	1092 (87.9%)	1092 (87.6%)
Black	14 (4.6%)	12 (3.9%)	90 (7.2%)	94 (7.5%)
Asian/Oriental	24 (7.9%)	23 (7.6%)	47 (3.8%)	49 (3.9%)
Other	4 (1.3%)	5 (1.6%)	13 (1.0%)	11 (0.9%)
Ethnicity [n (%)]				

Toujeo, insulin glargine [rDNA origin] injection, 300 Units/mL

Hispanic	15 (4.9%)	12 (3.9%)	214 (17.2%)	221 (17.8%)
Not Hispanic	289 (95.1%)	292 (96.1%)	1028 (82.8%)	1024(82.2%)
Region [n (%)]				
North America	214 (70.4%)	197 (64.8%)	695 (56.0%)	719 (57.7%)
Western Europe	28 (9.2%)	38 (12.5%)	100 (8.1%)	104 (8.3%)
Eastern Europe	38 (12.5%)	47 (15.5%)	337 (27.1%)	309 (24.8%)
Rest of the world	24 (7.9%)	22 (7.2%)	110 (8.9%)	114 (9.1%)
Region [n (%)]				
US	202 (66.4%)	187 (61.5%)	597 (48.1%)	647 (51.9%)
Non-US	102 (33.6%)	117 (38.5%)	645 (51.9%)	599 (48.1%)
Baseline weight (kg)				
Mean (SD)	81.9 (20.0)	81.8 (17.0)	99.9 (22.9)	99.9 (21.7)
Median	79.6	79.0	97.0	98.0
Min : Max	44 : 147	43 : 134	43 : 209	48 : 190
Baseline BMI (kg/m <sup>2</sup> )				
Mean (SD)	27.6 (5.4)	27.5 (4.8)	34.7 (6.9)	34.8 (6.4)
Median	27.2	26.9	33.7	34.2
Min : Max	17 : 51	19 : 48	18 : 63	20 : 62
Baseline BMI categories (kg/m <sup>2</sup> ) [n(%)]				
<25	99 (32.6%)	108 (35.5%)	64 (5.2%)	46 (3.7%)
[25-30[	118 (38.8%)	114 (37.5%)	263 (21.2%)	246 (19.7%)
[30-40[	77 (25.3%)	74 (24.3%)	654 (52.7%)	710 (57.0%)
≥40	10 (3.3%)	8 (2.6%)	261 (21.0%)	244 (19.6%)
Baseline eGRF (mL/min/1.73m <sup>2</sup> )				
Mean (SD)	82.47 (19.78)	82.14 (19.13)	79.06 (20.52)	78.77 (20.85)
Median	82.01	81.99	78.35	78.42
Min : Max	25.3 : 150.8	25.1 : 145.9	19.9 : 155.3	15.0 : 172.2
Baseline eGFR categories (mL/min/1.73m <sup>2</sup> ) [n(%)]				
≥90	107 (35.2%)	90 (29.6%)	334 (26.9%)	349 (28.0%)
[60-90[	159 (52.3%)	178 (58.6%)	701 (56.4%)	685 (55.0%)
[30-60[	35 (11.5%)	34 (11.2%)	200 (16.1%)	199 (16.0%)
<30	3 (1.0%)	2 (0.7%)	7 (0.6%)	13 (1.0%)
Randomization strata of screening HbA1c (%) [n(%)]				
<8	128 (42.1%)	128 (42.1%)	427 (34.4%)	432 (34.7%)
≥8	176 (57.9%)	176 (57.9%)	815 (65.6%)	814 (65.3%)
Randomization strata of geographical region <sup>b</sup> (%) [n(%)]				

Number	274	275	435	438
Japan	24 (8.8%)	22 (8.0%)	25 (5.7%)	25 (5.7%)
Non-Japan	250 (91.2%)	253 (92.0%)	410 (94.3%)	413 (94.3%)

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Source: ISS, Table 25

**Reviewer’s comment:**

**The proportion of patients with (HbA1c  $\geq$  8%) in both T1DM and T2DM study populations adequately represent the overall population in regards to severity of diabetes. However, there are limitations in how the study populations do not represent some subgroups appropriately due to low number of enrollees. These groups include:**

- 1. Patients Ages  $\geq$ 65 years of age in the T1DM population (~10% of those enrolled)**
- 2. Black and Asian races in both T1DM and T2DM pools (~10% of those enrolled in each drug group)**
- 3. Patients with GFR $<$ 60 mL/min/1.73m<sup>2</sup> (~less than 20% of those enrolled in each drug group)**

**Of these limitations, the most notable is the lack of representation of Black patients in all study populations, since African American patients are disproportionately affected by diabetes and its complications compared to Caucasians<sup>1</sup>. I am in agreement with Dr. Kettermann’s review, in that “although the trends in noninferiority were similar among different races, sample sizes were too small to produce robust conclusions for non-whites.”**

### **7.2.2 Explorations for Dose Response**

Both HOE901-U300 and Lantus were titrated to glycemic goals; explorations of dose response are not applicable.

### **7.2.3 Special Animal and/or In Vitro Testing**

None

### **7.2.4 Routine Clinical Testing**

Routine clinical testing included the safety assessments as described in section 5 of this review. Each clinical trial had routine testing measures at specified intervals. For listing of specific tests, see Table 69. Routine clinical testing was adequate to assess the safety of the drug under review.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

See section 4 – Clinical Pharmacology

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

Hypoglycemia is the major adverse event associate with insulin use. Hypoglycemia is reviewed in sections 6 and 7.3.4.

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<sup>1</sup> [http://www.cdc.gov/diabetes/statistics/complications\\_national.htm](http://www.cdc.gov/diabetes/statistics/complications_national.htm)

Immune reactions are also potential adverse events associated with insulin use. Immunogenicity was assessed by antibody measurements and is discussed in section 7.4.6.

## 7.3 Major Safety Results

### 7.3.1 Deaths

#### Phase 1

At the time of NDA submission, no deaths were reported during the Phase 1 program.

#### Pooled Phase 2/3 studies

Up to the dossier cut-off (29 October 2013), in the Phase 2/3 pool there were 13 deaths reported during the on-study period when pooling T1DM and T2DM patients (Table 42). Eight of these were in the HOE901-U300 group and five were in the Lantus group (0.5% in HOE901-U300 and 0.3% in Lantus group). The causes of deaths are listed in Table 42. In both groups, causes of death span multiple SOCs.

There were four additional deaths reported after the dossier cut-off date that were not included in the pooled safety analysis. Two of these deaths were in the HOE901-U300 and two in Lantus group.

In the 120—Day Safety Update Report, one death, in the ongoing 6-month safety extension period of Study EFC12449, was reported in the Lantus group.

**In total** (sum of deaths in main-on treatment period, post-dossier cut-off, and 120-Day safety report), there were 10 deaths in the HOE901-U300 vs. eight deaths in the Lantus group.

**Table 42 – Patient deaths for HOE901-U300 and Lantus up to the cutoff date of 29 October 2013**

Trial/Patient Number	Age (years)	Sex	Diabetes Type	Total Daily Dose (documented dose)	Last Day of IMP receipt/ death day	Description, cause of death
<b>Lantus</b>						
011628348003006 <sup>a</sup>	55	F	2	Glargine:99 U (day 160) Glulisine 54 U	160/161	Toxicity to Various agents (intoxication with medication)
011628428003009 <sup>b</sup>	56	M	2	Glargine: 57U (day 119) Glulisine:120 U	Unknown/172	Diabetes mellitus inadequate control, diabetic nephropathy, chronic renal failure
011628840058002	70	M	2	Glargine: 114U Metformin 1700mg Aspart: 95 U	311/312	Cardio-respiratory arrest
011629642006008	66	F	2	Glargine: 48U (day 305)	305/314	Acute myocardial infarction
011629643009018 <sup>d</sup>	50	F	2	Glargine:144U (day78) Rescue insulin 30 U* (day 137)	78/153	Pyelonephritis chronic
<b>HOE901-U300</b>						
011628528004001 <sup>c</sup>	65	M	2	Glargine: 84U (day 90) Aspart: 49U	160/172	Infective thrombosis
011628528008004 <sup>f</sup>	64	F	2	Glargine: 60U (day 105)- last known dose Aspart 44 U	120/203	Metastatic bronchial carcinoma
011628840041001g	65	M	2	Glargine: 123U (day 84)	84/88	Pulmonary embolism
011629276003007	68	F	2	Glargine:90 U (day 63) Metformin 2000 mg Sitagliptin 100 mg	63/65	Myocardial infarction
011629276008001	59	M	2	Glargine:60U (day180) Metformin 2550mg Glimepiride 6mg	182/183	Sudden cardiac death
011629840107001 <sup>e</sup>	50	F	2	Glargine 165U (day 268) Metformin 1700mg	268/269	Acute myocardial infarction
012347840257005	47	M	2	Glargine: 75U Metformin 2000 mg	57/58	Arteriosclerosis coronary artery disease (MACE)
12456840426008	57	M	1	Glargine: 30 U (day 119) Lispro: 30U	119/120	Coronary artery disease (MACE)

<sup>a</sup> Patient also experienced the following SAEs: depression

<sup>b</sup> Patient also experienced the following SAEs: Osteomyelitis, cellulitis, sepsis, hypoglycemia, diabetic neuropathy, chronic cardiac failure, wound infection, cerebral ischemia

<sup>c</sup> Patient also experienced the following SAEs: diabetic foot, sepsis, endocarditis, septic embolus

<sup>d</sup> Patient also experienced the following SAE/MACE: ischemic stroke

\*insulin type not specified

<sup>e</sup> Patient also experienced the following SAE: cardiac failure congestive

<sup>f</sup> Patient also experienced the following AE: Wheezing

<sup>g</sup> Patient also experienced the following SAE/AE leading to treatment discontinuation: Osteoarthritis

### Summary of Narratives:

Narratives up to cutoff date of October 29, 2013 are summarized below. Narratives post-dossier cut-off follow these.

#### 011628348003006

55 year-old white woman, randomized to Lantus (evening), baseline HbA1c 7.4%, had a history of T2DM since 2003. Diabetic history was complicated by depression, hyperlipidemia, and hypertension. On Day 156 patient reported a new AE of moderate intensity recurrent **Depression**. Patient was started on venlafaxine hydrochloride (Olwexya), clonazepam and venlafaxine hydrochloride (Rivotril). On Day 161, the patient was reported to have intoxication with medications (**Toxicity to various agents**) which led to treatment discontinuation. The IMP was permanently discontinued on Day 160. The patient died on Day 161 autopsy was performed and suicide with medication was confirmed.

#### 011628428003009

56 year-old white man, randomized to Lantus (evening), with baseline HbA1c 9.1%, had a history of T2DM since 1982. Diabetic history included diabetic retinopathy and nephropathy with proteinuria. Other medical history between 2007 and 2010 included: osteomyelitis, chronic renal failure, cardiac failure, and hypertension. On Day 16 patient had an SAE of **osteomyelitis** of his second left toe, which led to amputation of the toe. On Day 67, the patient developed **Cellulitis** and **Sepsis** from previous wound site. Unspecified corrective treatment was provided and patient recovered from sepsis on Day 76. On day 171, at an unspecified time, the patient experienced an episode of symptomatic hypoglycemia requiring assistance (SMPG 37.98 mg/dL). IV glucose was used for treatment of hypoglycemia with improvement of symptoms. The date and time of the last administration of basal and mealtime insulin prior to episode were not reported. On Day 171 of the study, the patient was also found to have new SAEs including: chronic heart failure (NYHA IV) (**Cardiac failure chronic**), diabetes mellitus insulin dependent decompensated (**Diabetes mellitus inadequate control**), diabetic nephropathy (stage 5), (**Diabetic nephropathy**)/ chronic kidney failure stage 4 with acute decompensation (**Renal failure chronic**), **diabetic neuropathy**, foot **Wound infection**, and decompensated chronic cerebrovascular ischemia (**Cerebral ischemia**). The events led to treatment discontinuation and hospitalization. During hospitalization, patient received glucose, antibiotics, and analgesics. Patient was found to have cardiomyopathy on chest X-ray. On Day 172 patient had, asystole and resuscitation measures failed. Autopsy was not performed. Upon medical review, it was confirmed that the event **Cardiac failure chronic** was to be considered a major CV event.

**Reviewer's comment: it is possible that the event of severe hypoglycemia contributed to the patient's acute decompensation, but it is unclear from the narrative.**

#### 011628528004001

Patient was a 65-year-old white male with a history of T2DM for 12 years complicated by diabetic retinopathy, sensory/motor neuropathy, and nephropathy. Other medical history included coronary artery bypass (2007), aortic valve replacement (2007) and history of angina pectoris. Patient was randomized to the HOE901-U300 (evening) arm. On day 110, the patient had a worsening of an ongoing **diabetic foot** wound that required hospitalization for ulcer and

antibiotic treatment. On day 160, the patient was hospitalized for staphylococcus aureus **sepsis**. IMP was discontinued on Day 160 and replaced with infusion of aspart. On day 161, he was diagnosed with **endocarditis** of aortic valve prostheses. On day 162, he was diagnosed with left and right cerebellar **septic embolus**. Patient was diagnosed with infected thrombosis and embolism in the heart (**Infective thrombosis**) and after persistent confusion, pupillary differences, and persistent abscesses, the patient died on Day 172.

**Reviewer's comments: the clinical presentation at the time of death (confusion and pupillary differences) can be reasonably attributed to septic brain emboli.**

**011628528008004**

64-year-old woman was randomized to HOE901-U300 (evening) (b) (6). Patient had a baseline HbA1c of 7.2%, and a history of T2DM since 1998. Medical comorbidities included acute coronary syndrome (2010). On Day 27 the patient complained of AE of moderate intensity (**Wheezing**) which was treated with steroids. No action was taken with IMP. On Day (b) (6) the patient had an SAE of a (**fall**) associated with dizziness, headaches and constipation, which led to hospitalization. Relevant concomitant medications included antihypertensives, diuretics, anticoagulants, and analgesics. No corrective treatment was given. No action was taken with the IMP. The patient was considered to have recovered from the event on Day (b) (6) without sequelae. On day (b) (6) the patient was diagnosed with (**Metastatic bronchial carcinoma**) and was hospitalized the following day for varied complaints including constipation, orthostatic hypotension (spironolactone was discontinued) confusion and slowness. Post a fall the patient had a brain CT that revealed multiple intracranial metastases. Further workup revealed diffuse metastatic disease. Dexamethasone was started for cerebral metastases. IMP was discontinued on Day (b) (6). Patient died on Day (b) (6). It is unknown if an autopsy was performed. The immediate cause of death was metastatic bronchial carcinoma.

**Reviewer's comment: The exposure to the IMP seems too short to have been contributory given the diffusely metastatic bronchial carcinoma.**

**011628840041001**

65 year old Black man, randomized to HOE901-U300 (evening) and baseline HbA1c of 9.7%, had a history of T2DM since 2003. Medical comorbidities included prostate cancer (2011), polyarthritis, renal failure (2003), colon cancer (2002), hypertension, and hyperlipidemia. On day 76, the patient had a new SAE of severe intensity of pain due to osteoarthritis of left knee (**Osteoarthritis**). Patient was hospitalized for total left knee replacement. Postoperatively patient developed increased serum creatinine, urinary retention, acute tubular necrosis, left knee pain, and fevers. Patient received treatment with correction of urinary retention. He was started on oral prednisone to relieve symptoms. He had left knee aspiration with positive monosodium irate crystals. IMP was permanently discontinued on Day 84. On day 88, the patient "experienced aspiration of severe intensity and died on the same day." No corrective treatment was given. The official cause of death was uncertain at the time of reporting. "Anatomic diagnoses were: peripheral pulmonary emboli, left ventricular cardiac hypertrophy, abdominal ileus, chronic pancreatitis, and prostatic hypertrophy." The cause of death was "Pulmonary

embolism" (**Pulmonary embolism**). No other diagnoses including pancreatitis appeared to have played any role in the patient's demise.

**011628840058002**

70 year old white male, randomized to Lantus (evening) and baseline HbA1c of 7.1%, had a history of T2DM since 1985. Comorbidities included diabetic sensory/motor neuropathy, hypertension, coronary artery disease (2006), right bundle branch block, sleep apnea, cerebrovascular accident and hyperlipidemia. On Day 312, the patient developed myocardial infarction leading to sudden cardiac death. It was not reported whether autopsy was performed. Last dose of IMP was on Day 311. Immediate cause of death was myocardial infarction leading to sudden cardiac death.

**011629276003007**

68 year old white woman, randomized to HOE901-U300 (evening) and baseline HbA1c of 7.1%, had a history of T2DM since 1999, complicated by diabetic retinopathy, hypercholesterolemia, hypertension, hypercoagulation and a history of pelvic venous thrombosis. On Day 65, the patient was found unconscious and apneic. Resuscitation efforts failed and cause of death, determined by the family doctor was thought to be due to pulmonary edema triggered by recent cardiac infarction. SAE of **Myocardial infarction** was recorded. Autopsy was not performed. Last IMP dose was on Day 63.

**011629276008001**

59 year old white man randomized to HOE901-U300 (evening) and baseline HbA1c of 8.1% had a history of T2DM since 1999. Patient's medical complications included macroangiopathy, myocardial infarction (2011), hypercholesterolemia, pneumonia, rheumatoid arthritis, obesity, and hypertension. On Day 183, the patient had **sudden cardiac death**. Autopsy was not performed.

**011629642006008**

66 year old white female randomized to Lantus (evening) with baseline HbA1c of 8%, had a history of T2DM since 1999. Medical comorbidities included diabetic retinopathy, diabetic sensory/motor neuropathy, macroangiopathy, myocardial infarction (2012) and dyslipidemia. On Day 306 the patient had an antero-lateral acute myocardial infarction (**Acute myocardial infarction**) with concurrent atrial fibrillation and hypoxia. Patient underwent treatment with inpatient diuresis and treatment with IV hydrocortisone. Shortly after admission to the ICU, the patient had cardiorespiratory arrest and as comatose due to hypoxia. Patient underwent supportive therapy in the ICU and treatment with antibiotic, antiarrhythmic, anticoagulant and diuretic treatment. Patient was subsequently diagnosed with pneumonia and antibiotic therapy was modified. On Day 309, patient required vasopressor support. Patient had a second cardiac arrest, refractory to resuscitation, (on Day 314), and was declared dead. IMP was permanently discontinued on Day 305.

**Reviewer's comments: The event of cardiorespiratory arrest appears to be secondary to overall decompensation after myocardial infarction.**

### **011629643009018**

50-year-old white woman was randomized to the Lantus (evening) on August 30, 2012. She had a baseline HbA1c of 9% and a history of T2DM since 2001. Medical comorbidities included diabetic retinopathy, diabetic sensory/ motor neuropathy, diabetic nephropathy, microalbuminuria, chronic pyelonephritis (August 2012), myocardial ischemia, cardiac failure, dyslipidemia and obesity. To intensify antidiabetic treatment, rescue therapy with rapid-acting insulin analogue 30U in addition to ongoing OAD and IMP was started on Day 137.

On Day 117, the patient had an **Ischemic stroke** in the branches of the left medial cerebral artery as well as hypertension. Upon review, it was confirmed that the event was to be considered a major CV event. On Day 149, the patient had exacerbation of chronic pyelonephritis (**Pyelonephritis chronic**) which was not responsive to antibiotic treatment. Patient died on day 153. Autopsy was performed but not available at the time of reporting.

### **011629840107001**

50 year old white woman randomized to HOE901-U300 (evening) with baseline HbA1c of 8.2% and T2DM since 1995. Medical comorbidities included diabetic retinopathy, diabetic sensory/motor neuropathy, diabetic nephropathy, hyperlipidemia, sleep apnea, congestive heart failure (since 2002), atrial fibrillation, and hypertension. On Day 149, the patient experienced worsening of congestive heart failure (**cardiac failure congestive**) with associated interstitial edema, which required hospitalization. Patient underwent diuresis and optimization of cardiac medications. No action was taken with the IMP.

On day 269 the patient had and **Acute myocardial infarction**, she was found deceased at home. The last IMP was taken on Day 268. No autopsy was conducted. The coroner assessed the cause of death as acute myocardial infarction.

**Reviewer's comment: The patient's HbA1c decreased from baseline of 8.2% to 6.0% at day 183 of study. FPG values recorded are 77.4 mg/dL, 50.4 mg/dL, and 127.8 mg/dL. IMP dose increased from an initial dose of 156 U to a maximal dose of 189 U with a last dose of 165U on day 268. There was an increase in IMP dose from 144 U on Day 227 to the final dose of 165 U on day 268. There is no clear evidence that hypoglycemia, given the increase in insulin doses and rapid control of HbA1c, contributed to the event of acute myocardial infarction that eventually led to the patient's death.**

### **012347840257005**

47 year old white man, randomized to HOE901-U300 (evening) with baseline HbA1c of 9.3%, had a history of T2DM since 2009. Medical comorbidities included: diabetic sensory/motor neuropathy, sleep apnea, peripheral edema, left ventricular hypertrophy, dyslipidemia, coronary artery arteriosclerosis, aortic valve replacement, hypertension, and obesity. Patient was a current smoker. On day 59, the patient had dyspnea and was transported to the hospital but then became unresponsive and nonresponsive to resuscitative measures. No autopsy was performed.

According to death certificate, the patient died from atherosclerotic heart disease (**Arteriosclerosis coronary artery**).

**12456840426008**

57-year-old Black male, randomized to HOE901-U300 (Morning) with baseline HbA1c of 8.3%, had a history of T1DM since 1988. Medical comorbidities included diabetic sensory/motor neuropathy, diabetic nephropathy, impaired renal function (Creatinine clearance<60ml/min) and hypertension. On day 120 the patient had chest pain but was unwilling to go to the hospital and patient was found deceased. Autopsy was performed and found hypertensive cardiovascular disease with concentric left ventricular hypertrophy and arteriolonephrosclerosis, decreased caliber of right and left dominant coronary arteries, minimal acute bronchopneumonia, pleural adhesions and hyperglycemia (postmortem glucose 659 mg/dL).

**Reviewer's comments: The postmortem severe hyperglycemia is unlikely due to the study drug.**

**Ongoing Studies:**

Death was reported for another four patients in the ongoing safety extensions of the studies EFC11628 and EFC 11629 See below for details. These deaths occurred after the dossier cutoff and are not part of the pooled safety database. One death was reported in the 120-Day Safety Report and is summarized below.

**011628348008008 (occurred after dossier cutoff date)**

57-year-old man was randomized to Lantus 63U. He had a history of T2DM complicated by left leg erysipelas, hypertension, hypertriglyceridemia, transient ischemic attack, post-thrombotic syndrome, chronic venous insufficiency, left foot big toe osteomyelitis, and left foot big toe amputation. The patient died suddenly due to myocardial infarction (determined from autopsy) 38 weeks after the first study drug intake.

**011628348014006 (occurred after dossier cutoff date)**

50-year-old man randomized to HOE901-U300 120 U for treatment of T2DM. His comorbidities included hepatic fibrosis, hypertension, and hyperlipidemia. Nine months after start of IMP, the patient developed shortness of breath, yellow sputum and was diagnosed with right sided pneumonia and CO2 retention. Patient was hospitalized intubated for 7 days and treated with antibiotics, steroids, diuretic, insulin, and anticoagulant therapy. 2 days post extubation he was found deceased; death was attributed to respiratory failure.

**011629840065006 (occurred after dossier cutoff date)**

57-year-old man randomized to HOE901-U300 for treatment of T2DM. His comorbidities included peripheral artery disease, skin ulcer (4th digit, left foot), hyperlipidemia, hypertension, right upper arm rash, heart murmur, and peripheral autonomic neuropathy due to diabetes mellitus, dysphagia, and smoking for 40 years. Eight months after starting study drug the patient was diagnosed with poorly differentiated adenocarcinoma of the esophagus with metastatic disease (Stage IV). Patient underwent radiation and chemotherapy. Patient stopped the study on month 9. On month 14, the patient died from adenocarcinoma of the esophagus.

**011628840001007 (occurred after dossier cutoff date)**

73-year-old male randomized to Lantus 129 U for treatment of T2DM. His comorbidities included diabetic nephropathy, obesity, hypertension, and sleep apnea. 9 months after the first study drug intake, the patient developed liver cancer and received treatment with chemotherapy. Patient died 2 months after this event. The investigator reported the cause of death was unknown, per obituary it was liver cancer.

**012449392109022 (occurred after dossier cutoff date- reported in 120-Day Safety Report)**

80-year-old male with T1DM, randomized to Lantus 14 U daily in addition to mealtime insulin. His comorbidities included hypothyroidism and lumbago. On [REDACTED] (b) (6) a suspected liver tumor was noticed on abdominal ultrasound and on [REDACTED] (b) (6) the patient was diagnosed with multiple **liver metastases**. Imaging confirmed that stomach was the primary cancer. The investigational product was permanently discontinued and the patient was withdrawn from the study. The patient died on [REDACTED] (b) (6). No autopsy was performed.

**Reviewer’s comments: Of all the patients exposed to HOE901-U300 who died during the clinical development program, the majority had T2DM (only 2 patients had T1DM). Most of the causes of death were due to cardiovascular disease. The deaths that occurred up to the dossier cutoff date seem mostly balanced between the comparator and the HOE901-U300 groups. After review of the narratives, this reviewer does not find any clear causality attributable to HOE901-U300.**

**7.3.2 Nonfatal Serious Adverse Events**

For definitions of adverse events, including serious adverse events (SAE) refer to section 7.1.2 Categorization of Adverse Events.

In this section, the reviewer evaluates the incidence of non-hypoglycemia-associated nonfatal SAEs within each pooled safety population (T1DM and T2DM) separately. Hypoglycemia-associated-SAEs and severe hypoglycemia are discussed in section 7.3.4 Significant Adverse Events.

Phase 1

Per the Sponsor, no nonfatal SAEs were reported during the Phase 1 program.

Phase 2/3 Pooled Safety Dataset – T1DM and T2DM Analyzed Separately

All nonfatal SAEs by primary SOC (System Organ Class) and PT (Preferred Term) during the main on-treatment period in the T1DM and T2DM pools analyzed separately are presented below in Table 43. Items in **bold** in the table are discussed in further detail in the reviewer’s comments.

**Table 43 - Nonfatal SAEs by primary SOC and PT during the main on-treatment period: T1DM and T2DM study pools - Safety population**

	T1DM	T2DM

<b>Primary System Organ Class Preferred Term n (%)</b>	<b>HOE901-U300 (N=304)</b>	<b>Lantus (N=304)</b>	<b>HOE901-U300 (N=1242)</b>	<b>Lantus (N=1246)</b>
Any class	18 (5.9%)	22 (7.2%)	65 (5.2%)	62 (5.0%)
Infections and infestations	3 (1.0%)	2 (0.7%)	14 (1.1%)	14 (1.1%)
Upper respiratory tract infection	0	0	0	1 (<0.1%)
Bronchitis	0	0	1 (<0.1%)	0
Urinary tract infection	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
Viral infection	1 (0.3%)	0	0	0
Pneumonia	0	0	0	3 (0.2%)
Cellulitis	0	0	0	1 (<0.1%)
Cystitis	0	0	1 (<0.1%)	0
Diverticulitis	0	0	1 (<0.1%)	1 (<0.1%)
Localized infection	0	0	0	1 (<0.1%)
Erysipelas	1 (0.3%)	0	1 (<0.1%)	0
Osteomyelitis	0	0	2 (0.2%)	1 (<0.1%)
Wound infection	0	0	1 (<0.1%)	0
Chronic sinusitis	0	0	1 (<0.1%)	0
Bronchopneumonia	0	0	1 (<0.1%)	0
Chronic tonsillitis	0	1 (0.3%)	0	0
Endocarditis	0	0	1 (<0.1%)	0
Groin abscess	0	0	1 (<0.1%)	0
Liver abscess	0	0	1 (<0.1%)	0
Postoperative wound infection	0	0	1 (<0.1%)	0
Pulmonary mycosis	0	0	1 (<0.1%)	0
Pyelonephritis	1 (0.3%)	0	0	0
Pyelonephritis acute	0	0	0	1 (<0.1%)
Sepsis	0	0	1 (<0.1%)	1 (<0.1%)
Septic embolus	0	0	1 (<0.1%)	0
Diabetic foot infection	0	0	0	1 (<0.1%)
Infected bites	0	0	0	1 (<0.1%)
Lung infection	0	0	0	1 (<0.1%)
Pyelonephritis chronic	0	0	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.3%)	6 (0.5%)	4 (0.3%)
Prostate cancer	0	0	2 (0.2%)	0
Benign neoplasm of thyroid gland	0	0	1 (<0.1%)	0
Breast cancer	0	0	1 (<0.1%)	0
Metastatic bronchial carcinoma	0	0	1 (<0.1%)	0
Myelodysplastic syndrome	0	0	1 (<0.1%)	0

Primary System Organ Class Preferred Term n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901- U300 (N=1242)	Lantus (N=1246)
Basal cell carcinoma	0	0	0	1 (<0.1%)
Chronic myeloid leukaemia	0	0	0	1 (<0.1%)
Intraductal proliferative breast lesion	0	0	0	1 (<0.1%)
Malignant melanoma	0	1 (0.3%)	0	1 (<0.1%)
Immune system disorders	1 (0.3%)	0	0	0
Hypersensitivity	1 (0.3%)	0	0	0
Metabolism and nutrition disorders	9 (3.0%)	13 (4.3%)	1 (<0.1%)	4 (0.3%)
Hypoglycemia	9 (3.0%)	12 (3.9%)	1 (<0.1%)	2 (0.2%)
Hyperkalemia	0	0	0	1 (<0.1%)
Dehydration	0	1 (0.3%)	0	0
Diabetes mellitus inadequate control	0	0	0	1 (<0.1%)
Diabetic ketoacidosis	0	1 (0.3%)	0	0
Psychiatric disorders	0	0	0	1 (<0.1%)
Depression	0	0	0	1 (<0.1%)
Nervous system disorders	2 (0.7%)	3 (1.0%)	5(0.4%)	9 (0.7%)
Diabetic neuropathy	0	1 (0.3%)	0	0
Hypoesthesia	0	0	0	1(<0.1%)
Hypoglycemic unconsciousness	1 (0.3%)	1 (0.3%)	2 (0.2%)	0
Syncope	0	0	1 (<0.1%)	2 (0.2%)
Convulsion	1 (0.3%)	0	0	0
<b>Transient ischemic attack</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1%)</b>	<b>0</b>
Cerebrospinal fluid leakage	0	0	1 (<0.1%)	0
Hypoglycemic seizure	1 (0.3%)	0	0	0
Loss of consciousness	1 (0.3%)	0	0	0
Aphasia	0	1 (0.3%)	0	0
<b>Cerebral infarction</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1%)</b>
<b>Cerebrovascular accident</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1%)</b>
Guillain-Barre syndrome	0	0	0	1 (<0.1%)
<b>Ischemic stroke</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>3 (0.2%)</b>
Eye disorders	0	0	0	1 (<0.1%)
Cataract	0	0	0	1 (<0.1%)

Primary System Organ Class Preferred Term n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901- U300 (N=1242)	Lantus (N=1246)
Cardiac disorders	2 (0.7%)	1 (0.3%)	16 (1.3%)	15 (1.2%)
Coronary artery disease	1 (0.3%)	0	3 (0.2%)	1 (<0.1%)
Cardiac failure congestive	0	0	2 (0.2%)	1 (<0.1%)
Atrial fibrillation	0	0	1 (<0.1%)	2 (0.2%)
Bundle branch block left	0	0	0	1 (<0.1%)
Myocardial infarction	0	0	2 (0.2%)	1 (<0.1%)
Acute coronary syndrome	0	0	1 (<0.1%)	0
Acute myocardial infarction	0	0	1 (<0.1%)	2 (0.2%)
Angina pectoris	0	1 (0.3%)	1 (<0.1%)	2 (0.2%)
Arteriosclerosis coronary artery	0	0	1 (<0.1%)	0
Atrioventricular block complete	1 (0.3%)	0	0	0
Cardiac disorder	0	0	1 (<0.1%)	0
Cardiac failure	0	0	1 (<0.1%)	1 (<0.1%)
Cardiovascular disorder	0	0	1 (<0.1%)	0
Myocardial ischemia	0	0	1 (<0.1%)	1 (<0.1%)
Ventricular tachycardia	0	0	1 (<0.1%)	0
Angina unstable	0	0	0	1 (<0.1%)
Aortic valve stenosis	0	0	0	1 (<0.1%)
Cardiac failure chronic	0	0	0	1 (<0.1%)
Nodal rhythm	0	0	0	1 (<0.1%)
Vascular disorders	1(0.3%)	1 (0.3%)	1(<0.1%)	2 (0.2%)
Hypertension	0	1 (0.3%)	0	0
Varicose vein	0	0	1 (<0.1%)	0
Hypotension	0	0	0	1 (<0.1%)
Femoral artery occlusion	1 (0.3%)	0	0	0
Aortic stenosis	0	0	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	0	0	4 (0.3%)	3 (0.2%)
Dyspnea	0	0	1 (<0.1%)	0
Asthma	0	0	1 (<0.1%)	0
Dyspnea exertional	0	0	1 (<0.1%)	0

Primary System Organ Class Preferred Term n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901- U300 (N=1242)	Lantus (N=1246)
Acute respiratory failure	0	0	1 (<0.1%)	0
Chronic obstructive pulmonary disease	0	0	0	2 (0.2%)
Acute pulmonary edema	0	0	0	1 (<0.1%)
Gastrointestinal disorders	1 (0.3%)	0	6 (0.5%)	3 (0.2%)
Abdominal pain	0	0	1 (<0.1%)	2 (0.2%)
Diverticulum intestinal	0	0	1 (<0.1%)	0
Duodenal ulcer	0	0	1 (<.1%)	0
Hemorrhoids	0	0	1 (<0.1%)	0
Ileus	0	0	1 (<0.1%)	0
Intestinal obstruction	1 (0.3%)	0	0	0
Lower gastrointestinal hemorrhage	0	0	1(<0.1%)	0
Colitis ischemic	0	0	0	1 (<0.1%)
Gastric ulcer hemorrhage	0	0	0	1(<0.1%)
Hepatobiliary disorders	0	0	1(<0.1%)	1 (<0.1%)
Cholelithiasis	0	0	0	1 (<0.1%)
Cholecystitis	0	0	1( <0.1%)	0
Skin and subcutaneous tissue disorder	0	0	2 (0.2%)	1 (<0.1%)
Skin ulcer	0	0	0	1 (<0.1%)
Diabetic foot	0	0	1 (<0.1%)	0
Urticaria	0	0	1 (<0.1%)	0
Musculoskeletal and connective tissue disorders	0	1 (0.3%)	6 (0.5%)	6 (0.5%)
Pain in extremity	0	0	1 (<0.1%)	0
Osteoarthritis	0	0	2 (0.2%)	2 (0.2%)
Flank pain	0	0	0	1 (<0.1%)
Musculoskeletal chest pain	0	0	1 (<0.1%)	1 (<0.1%)
Spinal osteoarthritis	0	0	1 (<0.1%)	0
Spondylitis	0	0	0	1 (<0.1%)
Rhabdomyolysis	0	0	1 (<0.1%)	0
Chondrocalcinosis pyrophosphate	0	0	0	1 (<0.1%)

Primary System Organ Class Preferred Term n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901- U300 (N=1242)	Lantus (N=1246)
Dupuytren's contracture	0	1 (0.3%)	0	0
Renal and urinary disorders	0	1 (0.3%)	4 (0.3%)	4 (0.3%)
Nephrolithiasis	0	0	1 (<0.1%)	1 (<0.1%)
Renal failure acute	0	0	1 (<0.1%)	0
Renal colic	0	0	1 (<0.1%)	0
Urinary retention	0	1 (0.3%)	0	0
Diabetic nephropathy	0	0	0	1 (<0.1%)
Renal failure chronic	0	0	0	2 (0.2%)
Urinary bladder polyp	0	0	1 (<0.1%)	0
Calculus urinary	0	0	0	1 (<0.1%)
Reproductive system and breast disorders	0	0	2 (0.2%)	1 (<0.1%)
Benign prostatic hyperplasia	0	0	0	1 (<0.1%)
Menorrhagia	0	0	1 (<0.1%)	0
Metrorrhagia	0	0	1 (<0.1%)	0
General disorders and administration site conditions	0	0	3 (0.2%)	1 (<0.1%)
Non-cardiac chest pain	0	0	1 (<0.1%)	1 (<0.1%)
Chest pain	0	0	1 (<0.1%)	0
Sudden cardiac death	0	0	1 (<0.1%)	0
Investigations	0	0	1 (<0.1%)	0
Alanine aminotransferase increase	0	0	1 (<0.1%)	0
Injury, poisoning and procedural complications	3 (1.0%)	1 (0.3%)	4 (0.3%)	5 (0.4%)
Contusion	0	0	1 (<0.1%)	0
Fall	0	0	2 (0.2%)	1 (<0.1%)
Limb injury	0	0	0	1 (<0.1%)
Meniscus injury	0	0	1 (<0.1%)	0
Overdose	2 (0.7%)	0	0	0
Accidental overdose	1 (0.3%)	0	0	0
Toxicity to various agents	0	0	0	1 (<0.1%)
Brain contusion	0	1 (0.3%)	0	0

Primary System Organ Class Preferred Term n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Open fracture	1 (0.3%)	0	0	0
Rib fracture	0	1 (0.3%)	0	0
Airway complication of anesthesia	0	0	0	1 (<0.1%)
Head injury	0	0	0	1 (<0.1%)
Pelvic fracture	0	1 (0.3%)	0	0
Subdural hematoma	0	1 (0.3%)	0	1 (<0.1%)
Thoracic vertebral fracture	0	1 (0.3%)	0	0
Surgical and medical procedures	0	0	0	1 (<0.1%)
Medical device removal	0	0	0	1 (<0.1%)

TEAE: treatment-emergent adverse event; SOC: system organ class; PT: preferred term; MedDRA 16.0 n (%): number and percentage of patients with at least one serious TEAE  
T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)  
T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347  
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT according to all TEAE summary in overall study pool. Source Table 60 ISS

### T1DM

In the T1DM safety pool, there was a lower incidence of SAEs in the HOE901-U300 vs. Lantus group (18 [5.9%] vs. 22 [7.2%] respectively). HOE901-U300 had higher incidence of overdose (HOE901-U300: 2 [0.7%] vs. 0 in Lantus). Upon review of the narratives for overdose SAEs, only one patient (012456348103004; see Table 64) overdosed with IMP (HOE901-U300). This patient overdosed on Day 1 of study, no other pertinent details are available. The other patient, 012456840412006, overdosed with NIMP (prandial) insulin on Day 45 after picking up the wrong pen. Both patients had T1DM.

For further discussion on overdose, see section 7.3.5 *Submission Specific Primary Safety Concerns*.

The incidence of nonfatal SAEs was mostly less than 1% in each SOC. Percentages  $\geq 1\%$  in any SOC included Metabolism and Nutrition Disorders ( $\geq 3\%$  for both groups) within which, numbers were higher in the Lantus group (13 [4.3%]) vs. the HOE901-U300 (9 [3%]). These included events of hypoglycemia, which are discussed in 7.3.4 Significant Adverse Events.

### T2DM

In the T2DM safety pool there was a slightly higher overall incidence of nonfatal SAEs in the HOE901-U300 vs. Lantus group (65 [5.2%]) vs. 62 [5.0%] respectively - see Table 43).

Incidence rates  $\geq 1\%$  occurred for the SOCs Infections and Infestations and Cardiac Disorders in both groups. One patient (011629840078004) was coded as having “Hypoesthesia” but should have been coded as having a transient ischemic attack, given the details of the narrative of hemiparalysis, and hypoesthesia that was transient.

**Reviewer’s comment: I count this patient as having a “TIA” in the comments below.**

When taken together, the Lantus T2DM group had a clustering of 6 similar terms categorized as: Cerebral infarction (1[ $<0.1\%$ ]), Cerebrovascular accident (1[ $<0.1\%$ ]), Ischemic stroke (3[ $<0.2\%$ ]) and hypoesthesia (1 [  $<0.1\%$ ]). The HOE901-U300 group had 1 event of TIA.

Of the reported SAEs, those numerically higher in the HOE901-U300 included Neoplasms Benign, Malignant and Unspecified, Cardiac Disorders, Skin and Subcutaneous Tissue Disorders, Reproductive System and Breast Disorders, and General Disorders and Administration Site Conditions. The imbalances were very small, however, and not likely to be clinically important. The greatest numerical imbalance not favoring U300 was observed in the Gastrointestinal Disorders SOC: there was twice the number of gastrointestinal disorders in the HOE901-U300 compared to the Lantus group (6 [0.5%] vs. 3 [0.2%] respectively). However, these spanned multiple Preferred Terms making a causal association unlikely.

**Reviewer’s comments: In the T1DM population, there is no apparent pattern of SAE differences between the HOE901-U300 and Lantus groups.**

**In the T2DM population, there is a greater number of cerebrovascular disorders (when the following PT terms are grouped together: cerebral infarction, cerebrovascular accident, ischemic stroke and TIA) in the Lantus compared to the HOE901-U300 group (6 events v. 1 respectively). The reason for this imbalance between groups is unknown. Review of narratives reveals that most patients with these cerebrovascular disorders (except for 1) had pre-existing conditions such as previous history of ischemic stroke or cerebrovascular accident predisposing them to these events.**

**Overall, review of all nonfatal serious adverse events submitted by the Sponsor did not raise other concerns (than those mentioned) of causality due to HOE901-U300 treatment.**

### **7.3.3 Dropouts and/or Discontinuations**

This section focuses on patient discontinuation due to adverse events.

#### Phase 1

In Phase 1 studies, 1 patient had an AE leading to treatment discontinuation. The patient was a healthy patient who had an episode of 4 ventricular extrasystoles while receiving Lantus 0.4 U/kg on day 8 of study.

#### Phase 2/3 Pooled Safety Dataset - T1DM Population

During the main on-treatment period the overall rate of patient treatment discontinuation was similar in both treatment groups: 14.5% in the HOE901-U300 group and 14.1% in the Lantus

group. Reasons for treatment discontinuation in the randomized T1DM population are summarized in Table 44. The rate of discontinuation due to adverse events was similar between groups. Specific adverse events leading to discontinuation are discussed later and shown in Table 49.

**Table 44 - Reasons for treatment discontinuation in the T1DM population - Randomized population**

	T1DM	
	HOE901-U300 (N=304)	Lantus (N=304)
Reason for main treatment period discontinuation		
Adverse event*	4 (1.3%)	5 (1.6%)
Lack of efficacy	4 (1.3%)	1 (0.3%)
Poor compliance to protocol	9 (3.0%)	4 (1.3%)
Other reasons	26 (8.6%)	33 (10.9%)
Missing^	1 (0.3%)	0

T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all Dosing regimens (morning or evening injection)

\*In an information request, the Sponsor clarified that a patient in the Lantus group discontinued treatment after the 6-month period due to neutropenia which occurred during the main on-treatment period, I count this patient in the Lantus group under discontinuation due to adverse event

^The patient listed as “Missing” reason, was clarified after database lock as “withdrew consent.”

Source: modified ISS Table 18

The category of “Other reasons” for discontinuation, in the randomized population, (Table 44) revealed the majority related to personal, family, or job conflicts with the study. Three patients (1 in HOE901-U300 and 2 in Lantus group) were listed under “Other reasons” for discontinuation but the reason provided suggests hypoglycemia. These three patients were not counted under the category of discontinuation due to adverse event by the Sponsor, because nonserious hypoglycemic events were not recorded as AEs.

**Reviewer’s comments: Even when recoding the 3 patients listed as discontinuing treatment due to “other reasons” as discontinuing due to “adverse event”, (i.e. 5/304 [1.6%] HOE901-U300 vs. 6/304 [2%] Lantus), the number of patients who overall discontinued due to adverse event remains balanced between the HOE901-U300 and Lantus group.**

Overall discontinuation of treatment in Phase 2/3 T2DM

During the main on-treatment period the overall rate of patient treatment discontinuation in the safety population was similar in both treatment groups: 128/1242, [10.3%] in the HOE901-U300 vs. 143/1246, [11.5%] in the Lantus group. TEAEs leading to treatment discontinuation were 1.7% (21/1242) in the HOE901-U300 vs. 1.4% (17/1246) in the Lantus group.

In Studies EFC11629 and EFC12347, patients who were not meeting glycemic targets after the titration period (i.e., after Week 12) were considered for initiation of rescue treatment. Patients starting rescue therapy were not considered as completing the main 6-month on-treatment period, but were included in the safety population and followed. The number of participants initiated on rescue therapy during the main 6-month period was similar between treatment groups (HOE901-U300: 2.4% vs. Lantus: 2.8%).

**Table 45 - Reasons for treatment discontinuation in the T2DM population - Safety population**

	<b>HOE901-U300 (N=1242)</b>	<b>Lantus (N=1246)</b>
Completed main treatment period	1084 (87.3%)	1070 (85.9%)
Permanently discontinued the main treatment period	128 (10.3%)	143 (11.5%)
Subject's request for treatment discontinuation	85 (6.8%)	98 (7.9%)
Rescue intake during main 6-month period <sup>a</sup>	30 (2.4%)	35 (2.8%)
Reason for main treatment period discontinuation		
Adverse event	21 (1.7%)	17 (1.4%)
Lack of efficacy	4 (0.3%)	5 (0.4%)
Poor compliance to protocol	12 (1.0%)	17 (1.4%)
Other reasons	91 (7.3%)	104 (8.3%)
Missing	0	0

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Percentages are calculated using the number of patients randomized as denominator. Patients are considered in the treatment group to which they were randomized

Patients who complete the main 6-month period are patients who did not permanently discontinued study treatment and who did not take any rescue medication.

<sup>a</sup>For studies EFC11629 and EFC12347 ONLY

Source: ISS Table 18

The “Other reasons” category in Table 45 was composed of the specific reasons listed in Table 46. There was no evident imbalance between the two insulins even when examining these “Other reasons.”

**Table 46 - Summary of “Other reasons” leading to treatment discontinuation for T2DM studies combined (EFC11628, EFC11629, and EFC12347)**

	HOE901-U300 N=91	Lantus N=104
Hypoglycemia (not reported as an AE unless serious, as per protocol)	3	5
Site closure	6	6
Diverse reasons(including patient no longer wanted to participate in study, traveling issues, conflict with job, diagnosed with T1DM, perceived lack of efficacy and discontinued due to site’s mistake)	61	64
Lost to follow-up	12	16
protocol violation	9	9
Insulin dropped below 39 units <sup>a</sup>	0	4
<sup>a</sup> For EFC11629 only		
<sup>b</sup> For EFC12347 only		

The types of TEAEs leading to treatment discontinuation did not have a clear trend apparent by SOC partition (see Table 47). There were no TEAEs leading to treatment discontinuation in the non-pooled studies.

**Table 47 - TEAEs leading to permanent treatment discontinuation by primary SOC during the main treatment period: T1DM and T2DM study pools - safety population**

Primary System Organ Class n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Any class	4 (1.3%)	5 (1.6%)	17 (1.4%)	16 (1.3%)
Infections and infestations	0	0	0	3 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2(0.2%)	1 (<0.1%)
Blood and lymphatic system disorders	1 (0.3%)	1 (0.3%)	1(<0.1%)	1 (<0.1%)
Metabolism and nutrition disorders	0	2 (0.7%)	0	2 (0.2%)
Psychiatric disorders	0	0	2(0.2%)	3 (0.2%)
Nervous system disorders	1 (0.3%)	0	2(0.2%)	2 (0.2%)
Cardiac disorders	1 (0.3%)	0	3(0.2%)	3 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (<0.1%)
Gastrointestinal disorders	0	0	2(0.2%)	0

Musculoskeletal and connective tissue disorders	0	0	1(<0.1%)	1 (<0.1%)
Renal and urinary disorders	0	0	1(<0.1%)	1 (<0.1%)
Pregnancy, puerperium and perinatal conditions	1 (0.3%)	0	0	0
General disorders and administration site conditions	0	0	2(0.2%)	3 (0.2%)
Investigations	0	1 (0.3%)	3(0.2%)	1 (<0.1%)
Injury, poisoning and procedural complications	0	1 (0.3%)	0	2 (0.2%)

n (%): number and percentage of patients with at least one TEAE leading to permanent treatment discontinuation T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Source: ISS, Table 62

**Reviewer’s comment:**

**There was no apparent imbalance between the rates of discontinuation in the HOE901-U300 group compared to the Lantus group due to adverse events in both the T1DM and T2DM pools. In those that discontinued due to adverse event, there is no apparent clustering of SOC to explain discontinuation.**

**7.3.4 Significant Adverse Events**

Hypoglycemia is a significant adverse event that occurs with all insulins. In this section, the reviewer evaluates the differences in incidence of hypoglycemia in HOE901-U300 compared to Lantus.

Prior to the submission of this NDA, there were multiple communications between the Agency and the Sponsor (b) (4)

[Redacted text block]

All phase 3 clinical trials had a Severe Hypoglycemia Review Board (SHRB). The SHRB was comprised of external experts who independently and blinded reviewed each event of severe and/or SAE hypoglycemia. None of the nonsevere hypoglycemic events was upgraded by the SHRB.

In the clinical trials submitted by the Sponsor, hypoglycemic events were defined as:  
**Severe hypoglycemia (as reported by investigator):**

- Event requiring assistance of another person to actively administer resuscitative actions (patient could not administer him/herself). Classification of hypoglycemia as severe, by investigators, was based on “assistance required” as reported in the e-CRF.
- Might be associated with sufficient neuroglycopenia to induce seizure, unconsciousness, or coma.
- Plasma glucose measurements might not be available, but neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose.

**Severe hypoglycemia (as classified by review board)**

- Event classified as severe by the Severe Hypoglycemia Review Board (SHRB) using the same ADA definition.

**Severe and/or confirmed hypoglycemia**

- Plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL), any severe (as reported by the investigator), documented symptomatic or asymptomatic hypoglycemic event as defined above (applicable only for Phase 2/3 studies).

**Documented symptomatic hypoglycemia:**

- is an event with typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL)

**Asymptomatic hypoglycemia:**

- Event without typical symptoms of hypoglycemia and a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL)

**Probable symptomatic hypoglycemia:**

- Event with typical symptoms of hypoglycemia without a plasma glucose determination; but was presumably caused by a plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL);
- symptoms treated with oral carbohydrate, glucagon or IV glucose and leading to significant improvement or prompt recovery

**Relative hypoglycemia:**

- event with typical symptoms of hypoglycemia, but with a measured plasma glucose concentration  $> 3.9$  mmol/L (70 mg/dL)

**Nocturnal hypoglycemia defined by time of the day**

- any hypoglycemia of the above first seven categories that occurred between 00:00 and 05:59 hours, regardless whether the patient was awake or woke up because of the event

**Nocturnal hypoglycemia defined by sleep status**

- Hypoglycemia of the above first seven categories waking the patient from sleep after having gone to bed in the evening and before getting up in the morning (before administration of any anti-hyperglycemic medication). This category applied only to studies PDY12777, EFC12347, and EFC12456.

**Daytime hypoglycemia**

- any hypoglycemia (defined by time of the day) of the first seven above categories that occurs between 06:00 and 23:59 hours (applicable only for Phase 2/3 studies).

**Reviewer’s comment: I have focused my review on significant adverse events defined as severe hypoglycemia (defined by the Sponsor), because this definition is the most specific, has clinical relevance and has precedence for labeling.**

**It should be noted that EFC12456 excluded patients who had severe hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before screening visit. Thus, this study excluded patients with known predisposition to frequent severe hypoglycemia.**

For each pivotal study, I focused my review on the following categories:

1. the number of patients with at least one episode of severe hypoglycemia (as reported by investigator)
2. the number of severe hypoglycemia events (as reported by investigator)
3. the time to occurrence of severe hypoglycemia (as reported by investigator)

T1DM (PDY12777 and EFC12456)

Summaries of the overall rate of each category/subcategory of hypoglycemia in T1DM for each trial are presented in Table 48.

EFC12456:

The number of patients who experienced at least one severe hypoglycemic event (as reported by investigator) in EFC12456, for all dosing regimens, i.e. night or day, was lower in the HOE901-U300 group, compared to the Lantus group (18/274, [6.6%] vs. 26/275 [9.5%] respectively).

PDY12777:

The number of patients who experienced at least one severe hypoglycemic event (as reported by investigator) in the PDY12777 group was lower in HOE901-U300 vs. Lantus (1/30, [3.3%] vs. 3/29, [10.3%] respectively).

**Reviewer's comments: PDY12777 was a small study with only 16-week duration that only showed a difference of two patients between drug arms in the incidence of severe hypoglycemia.**

(b) (4)

**Table 48 - Number (%) of patients with at least one hypoglycemia event during the main on-treatment period for all hypoglycemia categories: T1DM studies - Safety population**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Nocturnal hypoglycemia by sleep status <sup>a</sup>		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
<b>T1DM - EFC12456</b>								
<b>All dosing regimens</b>								
Number of patients	274	275	274	275	274	275	274	275
Any hypoglycemia	257 (93.8%)	258 (93.8%)	191 (69.7%)	196 (71.3%)	168 (61.3%)	157 (57.1%)	256 (93.4%)	254 (92.4%)
Severe hypoglycemia								
As per investigator	18 (6.6%)	26 (9.5%)	6 (2.2%)	7 (2.5%)	6 (2.2%)	5 (1.8%)	14 (5.1%)	19 (6.9%)
Documented symptomatic hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	233 (85.0%)	230 (83.6%)	162 (59.1%)	159 (57.8%)	151 (55.1%)	147 (53.5%)	229 (83.6%)	224 (81.5%)
< 3.0 mmol/L (54 mg/dL)	189 (69.0%)	192 (69.8%)	112 (40.9%)	107 (38.9%)	99 (36.1%)	109 (39.6%)	179 (65.3%)	173 (62.9%)
Asymptomatic hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	192 (70.1%)	209 (76.0%)	77 (28.1%)	96 (34.9%)	24 (8.8%)	26 (9.5%)	190 (69.3%)	203 (73.8%)
< 3.0 mmol/L (54 mg/dL)	93 (33.9%)	107 (38.9%)	27 (9.9%)	27 (9.8%)	11 (4.0%)	11 (4.0%)	91 (33.2%)	102 (37.1%)
Probable symptomatic hypoglycemia	21 (7.7%)	37 (13.5%)	10 (3.6%)	13 (4.7%)	10 (3.6%)	14 (5.1%)	16 (5.8%)	29 (10.5%)
Relative hypoglycemia								
> 3.9 mmol/L (70 mg/dL)	31 (11.3%)	24 (8.7%)	8 (2.9%)	11 (4.0%)	8 (2.9%)	10 (3.6%)	28 (10.2%)	18 (6.5%)
Severe and/or confirmed <sup>b</sup> hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	255 (93.1%)	257 (93.5%)	188 (68.6%)	193 (70.2%)	162 (59.1%)	155 (56.4%)	254 (92.7%)	253 (92.0%)
< 3.0 mmol/L (54 mg/dL)	214 (78.1%)	221 (80.4%)	127 (46.4%)	126 (45.8%)	105 (38.3%)	114 (41.5%)	205 (74.8%)	209 (76.0%)

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Nocturnal hypoglycemia by sleep status <sup>a</sup>		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
<b>T1DM - PDY12777</b>								
Number of patients	30	29	30	29	30	29	30	29
Any hypoglycemia	30 (100%)	29 (100%)	24 (80.0%)	27 (93.1%)	17 (56.7%)	21 (72.4%)	30 (100%)	29 (100%)
Severe hypoglycemia								
As per investigator	1 (3.3%)	3 (10.3%)	0	2 (6.9%)	0	0	1 (3.3%)	1 (3.4%)
Documented symptomatic hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	28 (93.3%)	28 (96.6%)	20 (66.7%)	23 (79.3%)	17 (56.7%)	19 (65.5%)	28 (93.3%)	27 (93.1%)
< 3.0 mmol/L (54 mg/dL)	25 (83.3%)	26 (89.7%)	15 (50.0%)	19 (65.5%)	12 (40.0%)	16 (55.2%)	25 (83.3%)	25 (86.2%)
Asymptomatic hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	26 (86.7%)	28 (96.6%)	12 (40.0%)	14 (48.3%)	3 (10.0%)	6 (20.7%)	26 (86.7%)	28 (96.6%)
< 3.0 mmol/L (54 mg/dL)	14 (46.7%)	17 (58.6%)	5 (16.7%)	8 (27.6%)	1 (3.3%)	5 (17.2%)	13 (43.3%)	15 (51.7%)
Probable symptomatic hypoglycemia	5 (16.7%)	8 (27.6%)	1 (3.3%)	3 (10.3%)	1 (3.3%)	3 (10.3%)	4 (13.3%)	6 (20.7%)
Relative hypoglycemia								
> 3.9 mmol/L (70 mg/dL)	0	2 (6.9%)	0	2 (6.9%)	0	1 (3.4%)	0	1 (3.4%)
Severe and/or confirmed <sup>b</sup> hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	30 (100%)	29 (100%)	24 (80.0%)	27 (93.1%)	17 (56.7%)	21 (72.4%)	30 (100%)	29 (100%)
< 3.0 mmol/L (54 mg/dL)	28 (93.3%)	28 (96.6%)	17 (56.7%)	25 (86.2%)	12 (40.0%)	18 (62.1%)	27 (90.0%)	28 (96.6%)

n (%): number and percentage of patients with at least one treatment-emergent hypoglycemia event

Studies included: 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

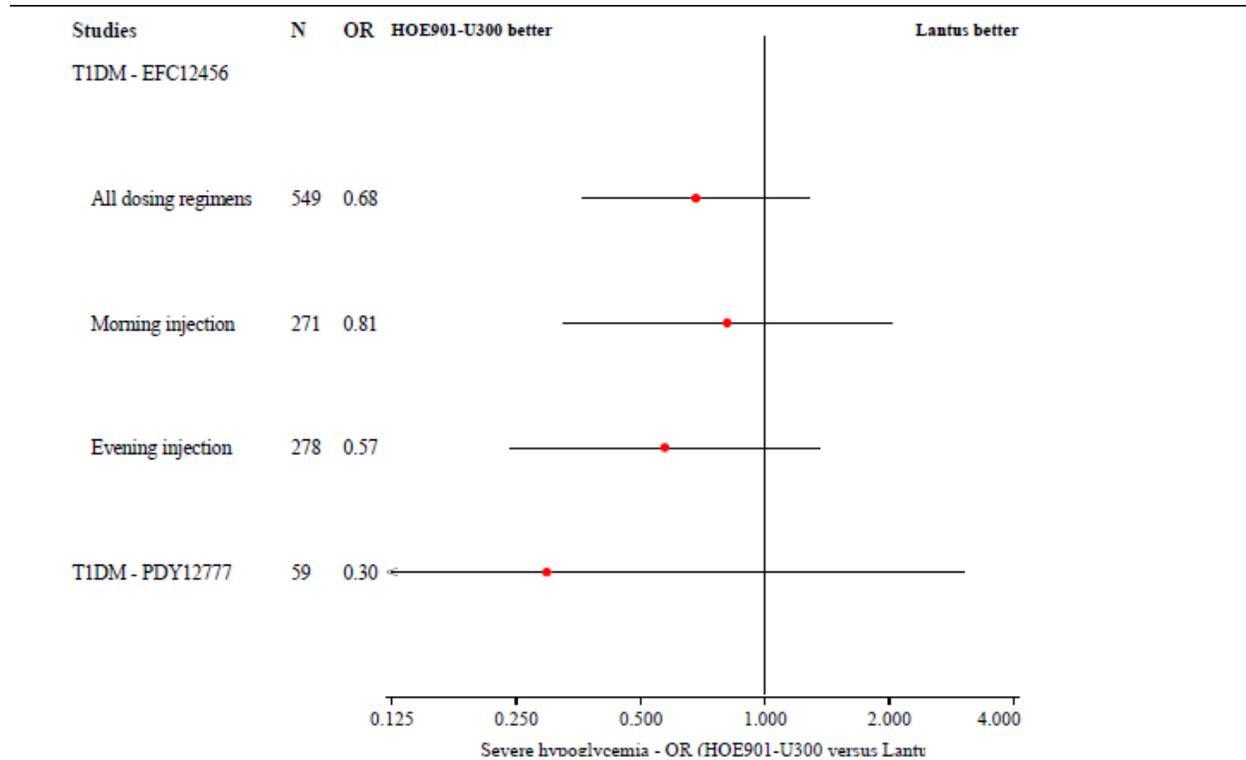
<sup>a</sup> Hypoglycemia waking the patient from sleep

<sup>b</sup> Severe and/or confirmed hypoglycemia: severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL))

Source: ISS Table 38

Figure 34 shows the sponsor’s analysis of patients with at least one severe hypoglycemia event during the main on-treatment period by time of dosing. There were no significant differences between treatment arms for any of the comparisons.

**Figure 33 - Forest plot of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator): T1DM studies- Safety population.**



Source: ISS, 3.1.4.1.

Both Figure 33 and Table 48 support the conclusion that the number of patients who experienced severe hypoglycemia in both HOE901-U300 and Lantus groups were not different. This similarity in hypoglycemia was also noted when examining the groups by morning or evening injection time and by incidence of nocturnal hypoglycemia. Specifically, the difference of nocturnal hypoglycemia between groups was only by one patient (HOE901-U300: 6 vs. Lantus: 7).

**Reviewer’s comments: The overall data shows that there is no difference in the overall hypoglycemia risk between HOE901-U300 and Lantus. These findings are consistent across all definitions of hypoglycemia (with slight differences in severe hypoglycemia by investigator) and throughout dosing regimens (morning vs. evening). The small numerical imbalance in patients experiencing severe hypoglycemia (as per investigator) favors HOE901-U300 in both T1DM studies. This difference in severe hypoglycemia should be evaluated cautiously, since the number of these events are small and could occur by chance.**

**When examining nocturnal hypoglycemia (alone) and nocturnal hypoglycemia by sleep status, the number patients differ only by one patient between treatment arms.** (b) (4)

**There is no statistical difference between these two groups** (b) (4)

**Furthermore, these hypoglycemia findings are not adjusted for the efficacy findings of the stud** (b) (4)

### *Event rate of hypoglycemia*

#### EFC12456:

In all dosing regimens, the exposure-adjusted event rate of severe hypoglycemia (as reported by investigator) was lower in the HOE901-U300 vs. Lantus group (for EFC12456: 30 per patient-year vs. 43 per patient-year; for PDY12777: 1 per patient-year vs. 3 per patient year respectively). See Table 49 for details. However, the lower event rate of severe hypoglycemia observed in the U300 arm is likely attributable to a higher rates of severe hypoglycemia in a few individual patients in the Lantus group. For example, evaluation of the narratives of patients who experienced severe hypoglycemia, confirmed that patient 012456840127002 was an outlier in the number of severe hypoglycemic events (14 recorded).

For other definitions of hypoglycemia, the data favor Lantus. See Table 49 for details.

#### PDY12777:

See Table 49 for details. The data are similar to the incidence rate analyses because it appears that the four reported severe hypoglycemia events were reported for four unique subjects. The relative risk of 0.30 favoring U300 is not statistically significant because of the wide confidence interval.

**Table 49 - Number of hypoglycemia events per patient-year during the main on-treatment period: T1DM studies-Safety population**

Type of hypoglycemia event	HOE901-U300	Lantus	RR versus Lantus	
	Number of events (rate per patient- year)	Number of events (rate per patient- year)	RR	95% CI
<b>T1DM - EFC12456</b>				
<b>All dosing regimens</b>				
Total patient-years	124.10	126.83		
Any hypoglycemia	9936 (80.06)	9380 (73.96)	1.09	(0.95 to 1.25)
Severe hypoglycemia <sup>a</sup>	30 (0.24)	43 (0.34)	0.74	(0.30 to 1.84)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	9732 (78.42)	9199 (72.53)	1.09	(0.94 to 1.25)
< 3.0 mmol/L (54 mg/dL)	2327 (18.75)	2302 (18.15)	1.04	(0.85 to 1.27)
<b>Morning injection</b>				
Total patient-years	61.09	62.58		
Any hypoglycemia	5006 (81.94)	4588 (73.32)	1.12	(0.92 to 1.36)
Severe hypoglycemia <sup>a</sup>	9 (0.15)	11 (0.18)	0.84	(0.18 to 3.89)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	4836 (79.16)	4487 (71.70)	1.10	(0.90 to 1.35)
< 3.0 mmol/L (54 mg/dL)	1120 (18.33)	1120 (17.90)	1.02	(0.77 to 1.37)
<b>Evening injection</b>				
Total patient-years	63.01	64.25		
Any hypoglycemia	4930 (78.24)	4792 (74.58)	1.06	(0.87 to 1.29)
Severe hypoglycemia <sup>a</sup>	21 (0.33)	32 (0.50)	0.66	(0.25 to 1.72)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	4896 (77.70)	4712 (73.34)	1.07	(0.88 to 1.31)
< 3.0 mmol/L (54 mg/dL)	1207 (19.16)	1182 (18.40)	1.05	(0.79 to 1.39)
<b>T1DM - PDY12777</b>				
Total patient-years	9.27	8.56		
Any hypoglycemia	1181 (127.40)	1237 (144.51)	0.89	(0.69 to 1.13)
Severe hypoglycemia <sup>a</sup>	1 (0.11)	3 (0.35)	0.30	(0.03 to 2.80)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	1173 (126.54)	1181 (137.97)	0.92	(0.72 to 1.18)
< 3.0 mmol/L (54 mg/dL)	282 (30.42)	395 (46.14)	0.66	(0.43 to 1.01)

RR: risk ratio

Studies included: 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

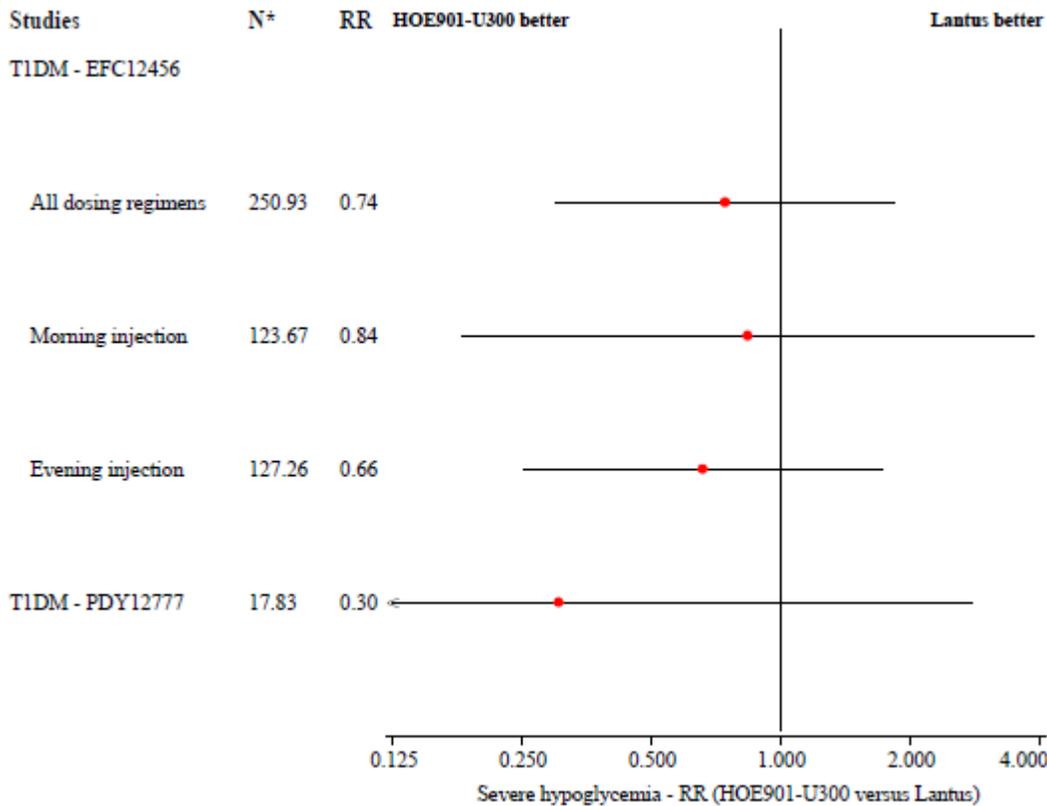
<sup>a</sup> Severe hypoglycemia: as per investigator; severe and/or confirmed hypoglycemia: severe and/or confirmed by plasma glucose ≤3.9 mmol/L (70 mg/dL) (resp. <3.0 mmol/L (54 mg/dL))

Note: RR based on overdispersed Poisson regression model with treatment and randomization strata of screening HbA1c (screening HbA1c categories for PDY12777) (<8.0 and ≥8.0%) as fixed effects, and logarithm of the

Source: ISS, Table 41

Figure 34 shows a forest plot of hypoglycemia events per patient-year that were severe (as per investigator) in the T1DM population. This figure shows that there is no difference between the two treatment groups in regards to hypoglycemia event rate.

**Figure 34 - Forest plot of number of hypoglycemia events per patient-year (severe hypoglycemia as per investigator) during the main-on treatment period: T1DM studies-Safety population**



Source ISS, 3.2.4.1

**Reviewer’s comments: Both Figure 34 and Table 48 provide evidence that there is no clear difference in the event rate of severe hypoglycemia between the two treatment groups (even when examining by morning or evening injection time).**

*Time to hypoglycemia*

During both the titration (first 8 weeks of treatment) and maintenance periods (week 9 to Month 6), there were less patients who experienced severe hypoglycemia (per investigator) in the HOE901-U300 vs. the Lantus group (see Table 50).

**Table 50 Number (%) of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by study period: T1DM EFC12456**

Severe hypoglycemia as per investigator	HOE901-U300	Lantus
	n(%)	n(%)
T1DM - EFC12456		
All dosing regimens		
Number of patients	274	275
Overall	18 (6.6%)	26 (9.5%)
Treatment Start to Week 8	9 (3.3%)	14 (5.1%)
From start of week 9 to Month 6	11 (4.0%)	14 (5.1%)

Source: ISS 3.3.5.1

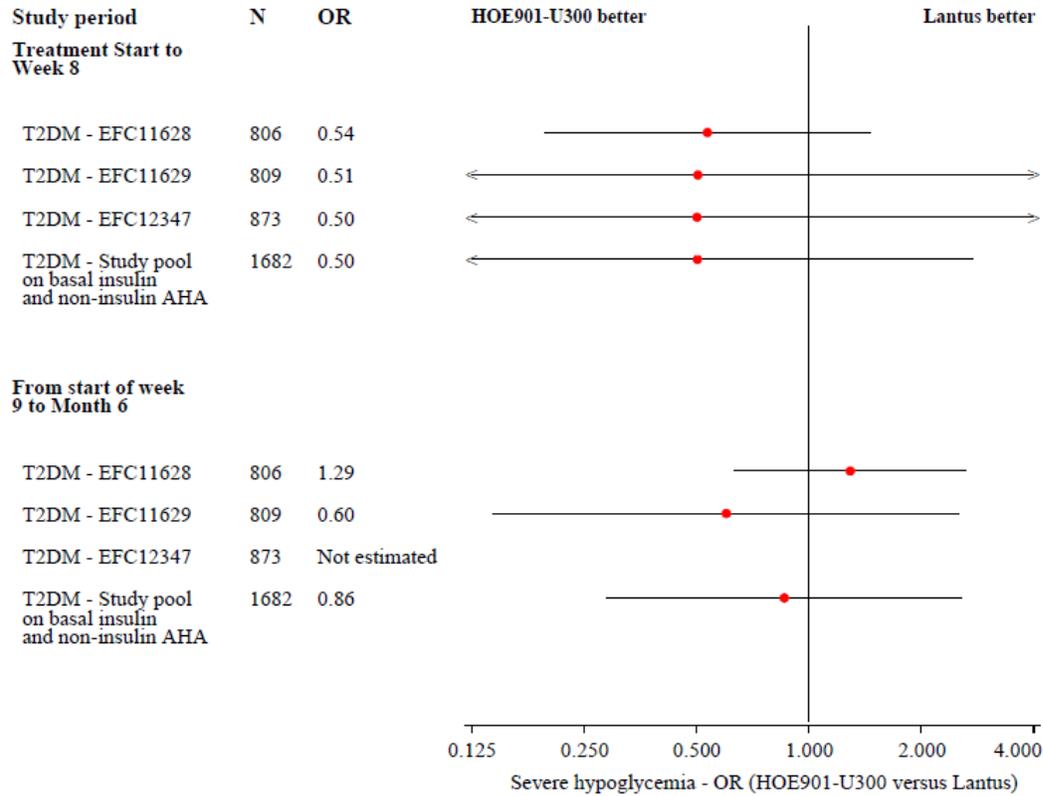
**Reviewer’s comment:** It is expected that the rate of hypoglycemia will be higher during times of insulin adjustment. There were fewer patients who experienced severe hypoglycemia (as per investigator) in the HOE901-U300 arm vs. the Lantus arm, more notably during the titration phase (initiation of therapy to week 8) than during the maintenance phase of the study (week 9 to Month 6). The lower patient incidence of severe hypoglycemia observed in the HOE901-U300 group may be due to the higher SMPG readings in the HOE901-U300 group compared to the Lantus group (see section 6 Review of Efficacy, Other Endpoints).

*T2DM (EFC11628, EFC11629 and EFC12347)*

Reference is made to Figure 35 (below) in this portion of the review. Figure 35 shows that across the three pivotal T2DM trials from treatment Start to Week 8 or from start of Week 9 to Month 6, there is no difference in severe hypoglycemia (as per investigator) between HOE901-U300 and Lantus. The forest plot also shows a sponsor created T2DM pool of subjects on basal insulin and non-insulin; however, this pooled group may not be appropriate because of design issues described in section 5 of this review. (Nevertheless, this pooled group analysis is consistent with the analyses of the individual trials).

While the data appear to numerically favor the HOE901-U300 group, notably from the trial period Start to Week 8, severe hypoglycemia is relatively rare among T2DM patients compared with T1DM patients, and the study was likely underpowered to detect any differences in severe hypoglycemia between study arms (note the wide confidence intervals in the forest plot). Further, of the two individual trial analyses shown for Week 8 to Month 6, one favors HOE901-U300 and the other favors Lantus. (b) (4)

**Figure 35 – Patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by study period: T2DM studies, safety population**



Source: ISS, Table in section 3.3.8.1

Detailed discussion of individual trials for T2DM  
EFC11628

*Patient incidence of hypoglycemia*

There was no meaningful difference between the patients who experienced severe hypoglycemia (as defined by the investigator), in the HOE901-U300 group compared to the Lantus group (20/404, [5%] vs. 23/402 [5.7%] respectively), refer to Table 51. When evaluating these events by time of day:

- Nocturnal hypoglycemia was seen in 2 more patients in the Lantus group than the HOE901-U300 group.
- Daytime hypoglycemia was seen in 1 more patient in the HOE901-U300 group than Lantus group

**Table 51 - Number (%) of patients with at least one hypoglycemia event during the main 6-month on –treatment period for all hypoglycemia categories: T2DM- EFC11628-Safety population**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
<b>T2DM - EFC11628</b>						
Number of patients	404	402	404	402	404	402
Any hypoglycemia	337 (83.4%)	356 (88.6%)	183 (45.3%)	240 (59.7%)	328 (81.2%)	345 (85.8%)
Severe hypoglycemia						
As per investigator	20 (5.0%)	23 (5.7%)	8 (2.0%)	10 (2.5%)	17 (4.2%)	16 (4.0%)
Documented symptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	283 (70.0%)	313 (77.9%)	145 (35.9%)	194 (48.3%)	265 (65.6%)	293 (72.9%)
< 3.0 mmol/L (54 mg/dL)	151 (37.4%)	167 (41.5%)	49 (12.1%)	68 (16.9%)	131 (32.4%)	141 (35.1%)
Asymptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	255 (63.1%)	274 (68.2%)	84 (20.8%)	102 (25.4%)	245 (60.6%)	263 (65.4%)
< 3.0 mmol/L (54 mg/dL)	69 (17.1%)	66 (16.4%)	9 (2.2%)	13 (3.2%)	67 (16.6%)	60 (14.9%)
Probable symptomatic hypoglycemia	18 (4.5%)	28 (7.0%)	6 (1.5%)	9 (2.2%)	15 (3.7%)	20 (5.0%)
Relative hypoglycemia						
> 3.9 mmol/L (70 mg/dL)	56 (13.9%)	76 (18.9%)	15 (3.7%)	33 (8.2%)	48 (11.9%)	60 (14.9%)
Severe and/or confirmed <sup>b</sup> hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	331 (81.9%)	353 (87.8%)	180 (44.6%)	231 (57.5%)	321 (79.5%)	339 (84.3%)
< 3.0 mmol/L (54 mg/dL)	181 (44.8%)	201 (50.0%)	63 (15.6%)	82 (20.4%)	164 (40.6%)	171 (42.5%)

Source ISS, modified Table 47

**Reviewer’s comments:**

**The small number of patients who experienced severe hypoglycemia (as reported by investigator) is not meaningfully different between groups, although smaller in the HOE901-U300 group. The incidence rate of nocturnal hypoglycemia is also not different between HOE901-U300 and Lantus.**

*Event rate of hypoglycemia*

Most of the events were driven by 2 patients: one on the HOE901-U300 group who had 11 severe hypoglycemic events and the other patient was on the Lantus group and had 18 severe hypoglycemic events.

However, the overall rate of severe hypoglycemia (as reported by investigator) by patient year was comparable between insulins (0.27 vs. 0.24 in HOE901-U300 vs. Lantus respectively).

Furthermore, the relative risk of severe hypoglycemia (as reported by investigator) was no different between treatment groups given the 95% confidence interval crossing 1.

**Reviewer’s comments:**

**More than twice as many patients experienced severe hypoglycemia in the EFC11628 than other T2DM studies. The higher number may be attributed to the severity of diabetes and difficulty with glucose control. Also the subjects in this trial were using prandial insulin which can independently contribute to hypoglycemia.**

*Time to hypoglycemia*

During the titration period (the first 8 weeks of treatment), there were fewer patients who experienced severe hypoglycemia (per investigator) in the HOE901-U300 vs. the Lantus group (6 vs. 11 respectively). However, from Week 9 to Month 6, there was a greater number of patients who had severe hypoglycemia (per investigator) in the HOE901-U300 group compared to the Lantus group (18 vs. 14 respectively). The number of patients who experienced nocturnal hypoglycemia was similar between treatment groups.

**Table 52 - Number (%) of patients with at least one hypoglycemia event during treatment start to Week 8 and Week 9 to Month 6 – EFC11628**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
T2DM - EFC11628						
Number of patients	404	402	404	402	404	402
Any hypoglycemia						
Overall	337 (83.4%)	356 (88.6%)	183 (45.3%)	240 (59.7%)	328 (81.2%)	345 (85.8%)
Treatment Start to Week 8	266 (65.8%)	311 (77.4%)	109 (27.0%)	150 (37.3%)	261 (64.6%)	301 (74.9%)
From start of week 9 to Month 6	306 (75.7%)	312 (77.6%)	151 (37.4%)	187 (46.5%)	293 (72.5%)	293 (72.9%)
Severe hypoglycemia						
As per investigator						
Overall	20 (5.0%)	23 (5.7%)	8 (2.0%)	10 (2.5%)	17 (4.2%)	16 (4.0%)
Treatment Start to Week 8	6 (1.5%)	11 (2.7%)	3 (0.7%)	3 (0.7%)	5 (1.2%)	8 (2.0%)
From start of week 9 to Month 6	18 (4.5%)	14 (3.5%)	5 (1.2%)	7 (1.7%)	16 (4.0%)	10 (2.5%)

Source: ISS, modified table 3.3.2.1

**Reviewer’s comment: Overall, the patient incidence of severe hypoglycemia (as per investigator) was numerically lower in the HOE901-U300 compared to the Lantus group. EFC11629:**

*Patient incidence of hypoglycemia*

There was no meaningful difference between the patients who experienced severe hypoglycemia (as defined by the investigator), in the HOE901-U300 group compared to the Lantus group (4/403, [1%] vs. 6/406 [1.5%] respectively). When evaluating these events by time of day:

- Nocturnal hypoglycemia was seen in 2 more patients in the Lantus group than the HOE901-U300 group.
- Daytime hypoglycemia was seen in 1 more patient in the Lantus group than the HOE901-U300 group

**Table 53 - Number (%) of patients with at least one hypoglycemia event during the main 6-month on –treatment period for all hypoglycemia categories: T2DM- EFC11629 - Safety population**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
T2DM - EFC11629						
Number of patients	403	406	403	406	403	406
Any hypoglycemia	288 (71.5%)	322 (79.3%)	123 (30.5%)	169 (41.6%)	273 (67.7%)	310 (76.4%)
Severe hypoglycemia						
As per investigator	4 (1.0%)	6 (1.5%)	0	2 (0.5%)	4 (1.0%)	5 (1.2%)
Documented symptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	200 (49.6%)	233 (57.4%)	91 (22.6%)	126 (31.0%)	176 (43.7%)	209 (51.5%)
< 3.0 mmol/L (54 mg/dL)	83 (20.6%)	109 (26.8%)	33 (8.2%)	47 (11.6%)	66 (16.4%)	87 (21.4%)
Asymptomatic hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	200 (49.6%)	238 (58.6%)	43 (10.7%)	77 (19.0%)	196 (48.6%)	237 (58.4%)
< 3.0 mmol/L (54 mg/dL)	43 (10.7%)	59 (14.5%)	10 (2.5%)	9 (2.2%)	37 (9.2%)	55 (13.5%)
Probable symptomatic hypoglycemia	6 (1.5%)	10 (2.5%)	3 (0.7%)	3 (0.7%)	3 (0.7%)	7 (1.7%)
Relative hypoglycemia						
> 3.9 mmol/L (70 mg/dL)	23 (5.7%)	45 (11.1%)	9 (2.2%)	23 (5.7%)	17 (4.2%)	34 (8.4%)
Severe and/or confirmed <sup>b</sup> hypoglycemia						
≤ 3.9 mmol/L (70 mg/dL)	282 (70.0%)	314 (77.3%)	114 (28.3%)	162 (39.9%)	270 (67.0%)	301 (74.1%)
< 3.0 mmol/L (54 mg/dL)	110 (27.3%)	143 (35.2%)	40 (9.9%)	54 (13.3%)	94 (23.3%)	121 (29.8%)

Source: ISS, modified Table 47

**Reviewer’s comments:** The number of patients who experienced severe hypoglycemia was small in both groups. There was no meaningful difference between HOE901-U300 and Lantus in regards to overall patient incidence of either severe hypoglycemia or nocturnal hypoglycemia, although numerically, the numbers favor HOE901-U300.

*Event rate of hypoglycemia*

In all dosing regimens, the overall rate of severe hypoglycemia (as reported by investigator) by patient year was comparable between insulins (0.03 vs. 0.06 in HOE901-U300 vs. Lantus respectively). Most of the events were driven by 1 patient on the Lantus group who had 6 severe hypoglycemic events.

The relative risk of severe hypoglycemia (as reported by investigator) was not statistically significantly different between treatment groups given the 95% confidence interval crossing 1. See Table 57.

*Time to hypoglycemia*

During the titration period and maintenance insulin dose periods, there were fewer patients who experienced severe hypoglycemia in the HOE901-U300 group compared to the Lantus group.

**Table 54 - Number (%) of patients with at least one hypoglycemia during treatment start to Week 8 and Week 9 to Month 6 – EFC11629**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
T2DM - EFC11629						
Number of patients	403	406	403	406	403	406
Any hypoglycemia						
Overall	288 (71.5%)	322 (79.3%)	123 (30.5%)	169 (41.6%)	273 (67.7%)	310 (76.4%)
Treatment Start to Week 8	198 (49.1%)	258 (63.5%)	58 (14.4%)	109 (26.8%)	187 (46.4%)	244 (60.1%)
From start of week 9 to Month 6	241 (59.8%)	267 (65.8%)	94 (23.3%)	119 (29.3%)	231 (57.3%)	257 (63.3%)
Severe hypoglycemia						
As per investigator						
Overall	4 (1.0%)	6 (1.5%)	0	2 (0.5%)	4 (1.0%)	5 (1.2%)
Treatment Start to Week 8	1 (0.2%)	2 (0.5%)	0	0	1 (0.2%)	2 (0.5%)
From start of week 9 to Month 6	3 (0.7%)	5 (1.2%)	0	2 (0.5%)	3 (0.7%)	4 (1.0%)

Source: ISS, modified Table 3.3.2.1

**Reviewer’s comment: There is no signal of increased incidence of severe hypoglycemia (per investigator) during the titration period in patients taking oral antihyperglycemic therapy and basal insulin when transitioned to either HEO901-U300 or Lantus.**

EFC12347:

*Patient incidence of hypoglycemia*

There was no difference between patients who experienced severe hypoglycemia (as defined by the investigator) between the HOE901-U300 and Lantus group (4, [0.9%] vs.4, [0.9%] respectively). There were no nocturnal hypoglycemia events in this trial.

**Table 55 - Number (%) of patients with at least one hypoglycemia event during the main 6-month on –treatment period for all hypoglycemia categories: T2DM- EFC12347-Safety population**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Nocturnal hypoglycemia by sleep status <sup>a</sup>		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
	T2DM - EFC12347							
Number of patients	435	438	435	438	435	438	435	438
Any hypoglycemia	217 (49.9%)	242 (55.3%)	88 (20.2%)	105 (24.0%)	60 (13.8%)	62 (14.2%)	207 (47.6%)	232 (53.0%)
Severe hypoglycemia								
As per investigator	4 (0.9%)	4 (0.9%)	0	0	0	0	4 (0.9%)	4 (0.9%)
Documented symptomatic hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	133 (30.6%)	157 (35.8%)	54 (12.4%)	68 (15.5%)	50 (11.5%)	59 (13.5%)	115 (26.4%)	141 (32.2%)
< 3.0 mmol/L (54 mg/dL)	33 (7.6%)	61 (13.9%)	14 (3.2%)	28 (6.4%)	12 (2.8%)	25 (5.7%)	23 (5.3%)	43 (9.8%)
Asymptomatic hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	137 (31.5%)	169 (38.6%)	44 (10.1%)	56 (12.8%)	7 (1.6%)	9 (2.1%)	134 (30.8%)	159 (36.3%)
< 3.0 mmol/L (54 mg/dL)	7 (1.6%)	8 (1.8%)	3 (0.7%)	1 (0.2%)	1 (0.2%)	0	5 (1.1%)	7 (1.6%)
Probable symptomatic hypoglycemia	11 (2.5%)	12 (2.7%)	1 (0.2%)	0	1 (0.2%)	0	10 (2.3%)	12 (2.7%)
Relative hypoglycemia								
> 3.9 mmol/L (70 mg/dL)	41 (9.4%)	48 (11.0%)	16 (3.7%)	11 (2.5%)	17 (3.9%)	9 (2.1%)	34 (7.8%)	40 (9.1%)
Severe and/or confirmed <sup>b</sup> hypoglycemia								
≤ 3.9 mmol/L (70 mg/dL)	201 (46.2%)	230 (52.5%)	78 (17.9%)	103 (23.5%)	51 (11.7%)	62 (14.2%)	190 (43.7%)	219 (50.0%)
< 3.0 mmol/L (54 mg/dL)	43 (9.9%)	71 (16.2%)	17 (3.9%)	29 (6.6%)	12 (2.8%)	25 (5.7%)	33 (7.6%)	53 (12.1%)

Source: ISS Table 4

Table 55 shows that the number of patients with severe hypoglycemia (as defined by the investigator) was not different between drug groups. In all cases the odds ratio and relative risk ratio show a clear lack of difference between the insulins (the confidence interval crosses 1), as per Figure 35.

#### *Event rate of hypoglycemia*

Each reported event occurred in a unique patient. The overall rate of severe hypoglycemia (as reported by investigator) by patient year was equal between insulins (0.02 in HOE901-U300 and Lantus respectively), see Table 57.

#### *Time to hypoglycemia*

During the titration period (treatment start to Week 8), there were fewer patients who experienced severe hypoglycemia as per investigator in the HOE901-U300 group compared to the Lantus group (1 vs 2 respectively) which reversed in the maintenance phase (3 vs. 2 respectively).

**Table 56 - Number (%) of patients with at least one hypoglycemia during treatment start to Week 8 and Week 9 to Month 6 – EFC12347**

Type of hypoglycemia event n(%)	All hypoglycemia		Nocturnal hypoglycemia (00:00-05:59)		Nocturnal hypoglycemia by sleep status <sup>a</sup>		Daytime hypoglycemia (06:00-23:59)	
	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus	HOE901-U300	Lantus
T2DM - EFC12347								
Number of patients	435	438	435	438	435	438	435	438
Any hypoglycemia								
Overall	217 (49.9%)	242 (55.3%)	88 (20.2%)	105 (24.0%)	60 (13.8%)	62 (14.2%)	207 (47.6%)	232 (53.0%)
Treatment Start to Week 8	118 (27.1%)	138 (31.5%)	38 (8.7%)	46 (10.5%)	16 (3.7%)	31 (7.1%)	106 (24.4%)	131 (29.9%)
From start of week 9 to Month 6	186 (42.8%)	210 (47.9%)	74 (17.0%)	77 (17.6%)	54 (12.4%)	43 (9.8%)	172 (39.5%)	199 (45.4%)
Severe hypoglycemia								
As per investigator								
Overall	4 (0.9%)	4 (0.9%)	0	0	0	0	4 (0.9%)	4 (0.9%)
Treatment Start to Week 8	1 (0.2%)	2 (0.5%)	0	0	0	0	1 (0.2%)	2 (0.5%)
From start of week 9 to Month 6	3 (0.7%)	2 (0.5%)	0	0	0	0	3 (0.7%)	2 (0.5%)

**Reviewer’s comments:**

**The number of patients who experienced severe hypoglycemia in the titration and maintenance phase was small in both groups.**

**Table 57 - Number of hypoglycemic events per patient-year during the main 6-month on-treatment period-T2DM studies-Safety population**

Type of hypoglycemia event	HOE901-U300	Lantus	RR versus Lantus	
	Number of events (rate per patient- year)	Number of events (rate per patient- year)	RR	95% CI
<b>T2DM - EFC11628</b>				
Total patient-years	194.86	193.40		
Any hypoglycemia	5138 (26.37)	5430 (28.08)	0.94	(0.80 to 1.11)
Severe hypoglycemia <sup>a</sup>	53 (0.27)	47 (0.24)	1.12	(0.42 to 3.00)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	4966 (25.48)	5176 (26.76)	0.95	(0.80 to 1.13)
< 3.0 mmol/L (54 mg/dL)	737 (3.78)	698 (3.61)	1.05	(0.78 to 1.41)
<b>T2DM - EFC11629</b>				
Total patient-years	191.33	193.80		
Any hypoglycemia	2750 (14.37)	3675 (18.96)	0.76	(0.62 to 0.93)
Severe hypoglycemia <sup>a</sup>	5 (0.03)	12 (0.06)	0.42	(0.07 to 2.40)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	2680 (14.01)	3516 (18.14)	0.77	(0.63 to 0.96)
< 3.0 mmol/L (54 mg/dL)	313 (1.64)	414 (2.14)	0.77	(0.52 to 1.13)
<b>T2DM - EFC12347</b>				
Total patient-years	200.98	197.73		
Any hypoglycemia	1431 (7.12)	1787 (9.04)	0.79	(0.61 to 1.02)
Severe hypoglycemia <sup>a</sup>	4 (0.02)	4 (0.02)	0.98	(0.23 to 4.23)
Severe and/or confirmed <sup>a</sup> hypoglycemia				
≤ 3.9 mmol/L (70 mg/dL)	1289 (6.41)	1681 (8.50)	0.75	(0.57 to 0.99)
< 3.0 mmol/L (54 mg/dL)	81 (0.40)	106 (0.54)	0.75	(0.47 to 1.22)

Source: ISS table 50

**Reviewer’s Comments for severe hypoglycemia in T1DM and T2DM studies:**

**The patient incidence of severe hypoglycemia numerically favored HOE901-U300 in four out of five trials (except for EFC12347, where numbers were identical in both treatment groups). The findings of the event rate of severe hypoglycemia was mixed. Two trials (EFC12456 and EFC11629) favored HOE901-U300; the results of trial EFC11628 favored Lantus; and the results in trial EFC12347 were identical between the two treatment groups. Because severe hypoglycemia is rare, and none of these studies is powered to detect a true difference between treatment groups, it is not out of the question that these findings may be due to chance. Hence, these findings should be interpreted cautiously.** <sup>(b) (4)</sup>

### 7.3.5 Submission Specific Primary Safety Concerns

The adverse events of special interest summarized in Table 58 are listed by the Sponsor. The search criteria for injection site reaction and hypersensitivity reaction were previously discussed and agreed to by the Agency.

**Table 58 - Adverse events of special interest**

Parameter	Definition
Injection site reactions	<p>Injection site reactions are identified using the following MedDRA searches:</p> <ul style="list-style-type: none"> <li>Under SOC General disorders and administration site conditions: HLTs Administration site reactions NEC (Not elsewhere classified), Injection site reactions, Infusion site reactions and Application and instillation site reactions under HLGT Administration site reactions</li> </ul>
Hypersensitivity reactions	<p>Hypersensitivity reactions are identified using the following MedDRA searches:</p> <ul style="list-style-type: none"> <li>Standardized MedDRA query (SMQ) Angioedema (Narrow), SMQ Severe cutaneous adverse reactions (Broad and Narrow), HLT Anaphylactic responses, and SMQ Hypersensitivity (Broad and Narrow).</li> </ul>
Cancers	<p>Cancers are identified using the following MedDRA searches: SMQ Malignancies (Narrow).</p>
CV events	<p>Clinical studies in the HOE901-U300 development program have not been prospectively designed to assess CV risk or to adjudicate major CV events, and therefore, given the study design, the number of CV events was expected to be low. Cardiovascular events are identified based on AEs or SAEs as reported by the investigator. The following CV events were considered:</p> <ul style="list-style-type: none"> <li>Cardiovascular death (identified using the following MedDRA searches with fatal outcome: all PTs under SOC Cardiac disorders; all PTs under SOC Vascular disorders; HLTs Cardiac device therapeutic procedures, Cardiac therapeutic procedures NEC and Cardiac valve therapeutic procedures under HLGT Cardiac therapeutic procedures; relevant PTs under HLT Death and sudden death; PT Apparent death under HLT General signs and symptoms NEC; and relevant PTs under HLT Cardiac and vascular procedural complications);</li> <li>Non-fatal myocardial infarction (MI) (identified using the following MedDRA searches: SMQ Myocardial infarction [Broad and Narrow]);</li> <li>Non-fatal stroke (identified using the following MedDRA searches: SMQ Hemorrhagic cerebrovascular conditions [Narrow]; and SMQ Ischemic cerebrovascular conditions [Narrow]).</li> </ul> <p>AEs identified using the above definition may include events that are not major adverse cardiovascular events (MACE). All cases identified will be presented in the ISS and relevant cases will be discussed with a conclusion whether they are considered MACE.</p>

Hepatic events	Hepatic events are identified using the following MedDRA search: SMQ Hepatic Disorder. Hepatic events, including biochemical Hy's Law cases, alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN), and ALT >10 x ULN, will be systematically evaluated.
Overdose	The reviewer searched the AE database as well as the narratives provided by the Sponsor using the PT term "overdose"
Hyperglycemia in the first week of switching to HOE901-U300	Hyperglycemia in the first week of therapy was evaluated by the Sponsor after request from the FDA due to concerns of decreased pharmacodynamic effect of HOE901-U300 compared to Lantus.

#### Local tolerability at injection site and hypersensitivity reactions

The overall numbers of injection site reactions in the T1DM and T2DM populations were low. There were a lower number of injection site reactions reported in the T1DM compared to the T2DM population. There was no injection site AE categorized as serious in either the T1DM or T2DM pool. One injection site related AE in the Lantus T2DM pool led to treatment discontinuation (patient 012347840233002 reported as injection site rash, after 5 days of treatment with resolution on Day 7).

In the T1DM population, injection site reactions were more common in the HOE901-U300 vs. the Lantus group (8, [2.6%] vs. 5, [1.6%] respectively). Most of these reactions were reported as PT term of site bruising in the HOE901-U300 vs. Lantus (5 [1.6%] vs. 2 [0.7%] respectively) followed by injection site pain (HOE901-U300: 3, [1%] vs. Lantus: 1, [0.3%]).

In the T2DM pool, the number of injection site reactions were lower in the HOE901-U300 group compared to Lantus (30, [2.4%] vs. 39, [3.1%] respectively). PT terms present greater in the HOE901-U300 group compared to the Lantus group included: injection site pruritus, injection site reaction, injection site discomfort, injection site hematoma, and injection site inflammation. The last 3 terms were each present as 1 TEAE vs. 0 in the Lantus group.

**Table 59 - Number (%) of patients experiencing at least one TEAE by prespecified MedDRA Queries and Preferred Term- Local tolerability injection site during the main on-treatment period- Safety population**

Preferred Term n(%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Any injection site reaction	8 (2.6%)	5 (1.6%)	30 (2.4%)	39 (3.1%)
Injection site bruising	5 (1.6%)	2 (0.7%)	9 (0.7%)	12 (1.0%)
Injection site pain	3 (1.0%)	1 (0.3%)	10 (0.8%)	13 (1.0%)
Injection site pruritus	0	0	4 (0.3%)	0
Injection site reaction	0	0	4 (0.3%)	2 (0.2%)
Injection site haemorrhage	0	0	3 (0.2%)	7 (0.6%)
Injection site discomfort	0	1 (0.3%)	1 (<0.1%)	0
Injection site erythema	0	1 (0.3%)	1 (<0.1%)	6 (0.5%)
Injection site haematoma	0	0	1 (<0.1%)	0
Injection site inflammation	0	0	1 (<0.1%)	0
Injection site irritation	0	0	1 (<0.1%)	1 (<0.1%)
Injection site oedema	1 (0.3%)	0	0	0
Infusion site haemorrhage	0	0	0	1 (<0.1%)
Injection site atrophy	0	0	0	1 (<0.1%)
Injection site induration	0	0	0	4 (0.3%)
Injection site rash	0	0	0	1 (<0.1%)
Injection site swelling	0	1 (0.3%)	0	1 (<0.1%)

TEAE: treatment-emergent adverse event; PT: preferred term; MedDRA 16.0

n (%): number and percentage of patients with at least one injection site reaction TEAE, based on SMQ and PT search

T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Source ISS: Table 63

**Reviewer's comment: The number of local injection site TEAEs were lower in HOE901-U300 compared to Lantus. There is no evident injection site safety signal that can be discerned from this data.**

#### Hypersensitivity reactions

See Table 58 for agreed MedDRA queries searched to identify hypersensitivity reactions listed in Table 60.

**Table 60 - Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term – Hypersensitivity reactions during the main 6-month period- Safety population**

	T1DM		T2DM	
	HOE901-U300	Lantus	HOE901-U300	Lantus

Preferred Term n (%)	(N=304)	(N=304)	(N=1242)	(N=1246)
Any hypersensitivity reactions	20 (6.6%)	14 (4.6%)	62 (5.0%)	55 (4.4%)
Rash	3 (1.0%)	0	10 (0.8%)	7 (0.6%)
Asthma	2 (0.7%)	0	6 (0.5%)	7 (0.6%)
Hypersensitivity	3 (1.0%)	0	3 (0.2%)	0
Pruritus	0	0	6 (0.5%)	3 (0.2%)
Seasonal allergy	3 (1.0%)	0	3 (0.2%)	4 (0.3%)
Dermatitis	0	1 (0.3%)	4 (0.3%)	3 (0.2%)
Erythema	1 (0.3%)	0	3 (0.2%)	4 (0.3%)
Blister	0	1 (0.3%)	3 (0.2%)	6 (0.5%)
Conjunctivitis	1 (0.3%)	3 (1.0%)	2 (0.2%)	4 (0.3%)
Dermatitis contact	0	0	3 (0.2%)	0
Pruritus generalized	1 (0.3%)	0	2 (0.2%)	1 (<0.1%)
Sneezing	1 (0.3%)	0	2 (0.2%)	0
Wheezing	1 (0.3%)	1 (0.3%)	2 (0.2%)	1 (<0.1%)
Drug hypersensitivity	1 (0.3%)	0	1 (<0.1%)	1 (<0.1%)
Eczema	1 (0.3%)	1 (0.3%)	1 (<0.1%)	3 (0.2%)
Rash generalized	1 (0.3%)	1 (0.3%)	1 (<0.1%)	0
Rhinitis allergic	0	2 (0.7%)	2 (0.2%)	3 (0.2%)
Skin exfoliation	0	0	2 (0.2%)	0
Acute respiratory failure	0	0	1 (<0.1%)	0
Allergic cough	0	0	1 (<0.1%)	0
Allergy to chemicals	0	0	1 (<0.1%)	0
Bronchial hyperactivity	0	0	1 (<0.1%)	0
Dermatitis exfoliative	0	0	1 (<0.1%)	0
Dermatitis infected	0	0	1 (<0.1%)	0
Drug eruption	0	1 (0.3%)	1 (<0.1%)	1 (<0.1%)
Eosinophilia	0	0	1 (<0.1%)	0
Flushing	0	0	1 (<0.1%)	1 (<0.1%)
Generalized edema	0	0	1 (<0.1%)	0
Gingival swelling	0	0	1 (<0.1%)	0
Rash erythematous	1 (0.3%)	0	0	0
Stomatitis	1 (0.3%)	0	0	0
Urticaria	0	0	1 (<0.1%)	1 (<0.1%)
Allergic sinusitis	0	0	0	1 (<0.1%)
Asthmatic crisis	0	0	0	1 (<0.1%)
Conjunctivitis allergic	0	1 (0.3%)	0	1 (<0.1%)

Dermatitis allergic	0	1 (0.3%)	0	2 (0.2%)
Injection site rash	0	0	0	1 (<0.1%)
Mouth ulceration	0	1 (0.3%)	0	0
Multiple allergies	0	1 (0.3%)	0	0
Neurodermatitis	0	0	0	1 (<0.1%)
Pruritus allergic	0	0	0	1 (<0.1%)
Rash pruritic	0	0	0	1 (<0.1%)
Rhinitis seasonal	0	0	0	1 (<0.1%)
Swelling face	0	0	0	1 (<0.1%)

TEAE: treatment-emergent adverse event; PT: preferred term; MedDRA 16.0

n (%): number and percentage of patients with at least one hypersensitivity reaction TEAE, based on SMQ and PT search

T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Source: modified ISS Table 65

Overall, the number of hypersensitivity reactions were higher in the HOE901-U300 (compared to Lantus) in both the T1DM and T2DM pools.

Specific SMQ searches were performed to better assess for imbalances between the two groups. When evaluating severe cutaneous reactions (Broad and Narrow SMQ), there were 2 vs. 6 reported events in the HOE901-U300 vs. Lantus group in the T1DM and 9 vs. 10 reported events in the HOE901-U300 vs. Lantus group in the T2DM population. When evaluating for Angioedema (Narrow SMQ), there were no cases reported in the T1DM and equal numbers (2 patients) reported in either HOE901-U300 or Lantus.

Three hypersensitivity events in the HOE901-U300 group were considered SAEs with the following narratives:

**011629642014005** – (PT term: urticaria-severe intensity) – 49 year old female who developed urticaria on day 99 of study after antibiotic therapy for acute laryngitis. During the hospitalization, she was diagnosed urinary tract infection with E. coli and trichomonas

**011629643013010** –(PT term: Asthma- moderate intensity)—48 year old female developed asthma after recovery of a common cold and use of mustard plasters on day 35 of study.

**012347840222011** -- (PT term: acute respiratory failure- severe intensity)-62 year old male with T2DM had an episode of acute respiratory failure of unknown etiology. Respiratory failure improved on the same day after hospitalization. The patient also had TEAEs of Blister (day 43) and SAE of musculoskeletal chest pain on day 84 of study.

No hypersensitivity reactions were reported during substudy EFC11629. One patient in substudy EFC11628 fixed dosing interval experienced an SAE episode of asthma after a viral infection.

**Reviewer’s comments:**

**There is an imbalance of unclear significance in the number of reported hypersensitivity PT terms (described in Table 60) with greater frequency in the HOE901-U300 group in both the T1DM and T2DM pools. This imbalance is not present when searching by severe cutaneous adverse reactions (Broad and Narrow SMQ) or by Angioedema (SMQ Narrow).**

**Although all SAE narratives of hypersensitivity were present in the HOE901-U300 group, there are alternative etiologies (such as initiation of antibiotic therapy or post-upper respiratory infection) for two of the three narratives presented. The etiology of the narrative of 012347840222011 does not clearly suggest a safety signal.**

**Overall, these findings are consistent with the existing label for hypersensitivity and allergic reaction of Lantus.**

Cancers

See Table 58 for MedDRA query strategy to identify cases of cancers. Using this query strategy, 16 patients with cancer were identified: 6 (0.4%) in the HOE901-U300 group and 10 (0.6%) in the Lantus group.

**Table 61 – Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term – Cancer during the main on-treatment period: T1DM and T2DM study pools- Safety population**

Preferred Term n (%)	T1DM		T2DM		ALL	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)	HOE901-U300 (N=1546)	Lantus (N=1550)
Any cancer	0	1 (0.3%)	6 (0.5%)	9 (0.7%)	6 (0.4%)	10 (0.6%)
Prostate cancer	0	0	2 (0.2%)	0	2 (0.1%)	0
Breast cancer	0	0	1 (<0.1%)	0	1 (<0.1%)	0
Metastatic bronchial carcinoma	0	0	1 (<0.1%)	0	1 (<0.1%)	0
Prostatic specific antigen increased	0	0	1 (<0.1%)	0	1 (<0.1%)	0
Squamous cell carcinoma	0	0	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Basal cell carcinoma (<0.1%)	0	0	0	1 (<0.1%)	0	1
Chronic myeloid leukemia	0	0	0	1 (<0.1%)	0	1 (<0.1%)
Intraductal proliferative breast lesion	0	0	0	1 (<0.1%)	0	1 (<0.1%)

Malignant melanoma	0	1 (0.3%)	0	1 (<0.1%)	0	2 (0.1%)
Squamous cell carcinoma of skin	0	0	0	3 (0.2%)	0	3 (0.2%)
Thyroid neoplasm	0	0	0	1 (<0.1%)	0	1 (<0.1%)

TEAE: treatment-emergent adverse event; PT: preferred term; MedDRA 16.0

n (%): number and percentage of patients with at least one cancer TEAE, based on SMQ search

T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

ALL: Including T1DM and T2DM studies

Source: ISS Table 67

In the T1DM population there was only one cancer identified during the 6-month on treatment period. This cancer was a case of malignant melanoma in the Lantus treatment group.

The remaining 15 malignancies were all in the T2DM safety pool (see Table 61). HOE901-U300 had a lower incidence of patients having cancer compared to Lantus (6, [0.5%] vs. 9, [0.7%] respectively).

#### Reviewer's comments:

**Overall, the number of cancers was small and there was no apparent trend/grouping in the types of cancers patients experienced. These cancers were broad in their type and did not suggest any safety signal related to the treatment group. However, it is important to keep in mind that the duration of treatment and follow-up in these trials were not conducted to detect these differences.**

#### MACE: Cardiovascular Death, non-fatal MI, non-fatal stroke

Refer to Table 58 for identification strategy of these events. Based on this search strategy, 26 patients reported 28 events during the main on-treatment period as MACE events. Refer to Table 62 for details. Note that there was **no** adjudication of these events.

**Table 62 – Number (%) of patients experiencing at least one TEAE by relevant Standardized MedDRA Queries and Preferred Term –Cardiovascular death, non-fatal MI, non-fatal stroke during the main on-treatment period –Safety population**

Preferred Term n (%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Any cardiovascular death, non-fatal MI, non-fatal stroke	1 (0.3%)	2 (0.7%)	9 (0.7%)	14 (1.1%)
Any cardiovascular death	1 (0.3%)	0	3 (0.2%)	1 (<0.1%)
Arteriosclerosis coronary artery	0	0	1 (<0.1%)	0

Coronary artery disease	1 (0.3%)	0	0	0
Myocardial infarction	0	0	1 (<0.1%)	0
Sudden cardiac death	0	0	1 (<0.1%)	0
Cardiac failure chronic	0	0	0	1 (<0.1%)
Any non-fatal MI	0	0	4 (0.3%)	4 (0.3%)
Acute coronary syndrome	0	0	1 (<0.1%)	0
Acute myocardial infarction	0	0	1 (<0.1%)	2 (0.2%)
Blood creatine phosphokinase increased	0	0	1 (<0.1%)	1 (<0.1%)
Myocardial infarction	0	0	1 (<0.1%)	1 (<0.1%)
Any non-fatal stroke	0	2 (0.7%)	2 (0.2%)	10 (0.8%)
Transient ischemic attack	0	0	2 (0.2%)	1 (<0.1%)
Carotid arteriosclerosis	0	0	0	1 (<0.1%)
Carotid artery stenosis	0	1 (0.3%)	0	0
Cerebral infarction	0	0	0	1 (<0.1%)
Cerebral ischemia	0	0	0	1 (<0.1%)
Cerebrovascular accident	0	0	0	1 (<0.1%)
Ischemic stroke	0	0	0	3 (0.2%)
Subdural hematoma	0	1 (0.3%)	0	1 (<0.1%)
Vascular encephalopathy	0	0	0	1 (<0.1%)
Vertebrobasilar insufficiency	0	0	0	1 (<0.1%)

MI: myocardial infarction; TEAE: treatment-emergent adverse event; PT: preferred term; MedDRA 16.0 n (%): number and percentage of patients with at least one cardiovascular TEAE, based on SMQ and PT search T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Source: ISS Table 69

Overall there was a greater incidence of any “cardiovascular death, non-fatal MI, non-fatal stroke” in the T2DM compared to the T1DM safety pool. Regardless of diabetes type (T1DM or T2DM), there was a higher number of events in the Lantus treatment group compared to HOE901-U300 group.

In the T1DM pool, the incidence of any MACE event was less than 1% in both treatment groups. None of the events reported in the Lantus group (due to carotid artery stenosis and subdural hematoma) were considered “serious” nor led to treatment discontinuation. The event of coronary artery disease in 1 patient, in the HOE901-U300 group, was serious, led to treatment discontinuation and death (narrative for patient 012456840426008 is in section 7.3.1 Deaths). Only this event was confirmed as MACE upon review of medical records. Despite this patient’s death being the only MACE event in the T1DM pool leading to death, the narrative of this patient does not suggest that HOE901-U300 caused his death.

The difference in MACE is more notable in the T2DM population (HOE901-U300: 9 [0.7%] vs. Lantus: 14 [1.1%]). The category, “Any non-fatal stroke” accounts for this imbalance, with 2 (0.2%) patients in the HOE901-U300 group compared to 10 (0.8%) in the Lantus group.

**Reviewer’s comment:**

**The imbalance in numbers due to “Any non-fatal stroke” favors HOE901-U300. Similar to the non-fatal serious adverse events in the T2DM group (see section 7.3.2), there is a clear imbalance in cerebrovascular disorders with a greater incidence in the Lantus compared to the HOE901-U300 group. In both HOE901 and Lantus, groups the patients who experienced these events had prior medical history that predisposed them to these events (such as prior myocardial infarction, hypertension, hyperlipidemia, coronary artery disease, arteriosclerosis). In essence, there is no MACE safety signal for HOE901-U300.**

Hepatic events

See Table 58 for MedDRA query strategy to identify how Sponsor classified cases of hepatic events. Refer to Table 63 for details regarding these events.

**Table 63 – Hepatic TEAEs by primary SOC and PT during the main on-treatment period: T1DM and T2DM study pools – Safety population**

Primary System Organ Class Preferred Term n(%)	T1DM		T2DM	
	HOE901-U300 (N=304)	Lantus (N=304)	HOE901-U300 (N=1242)	Lantus (N=1246)
Any class	4 (1.3%)	1 (0.3%)	6 (0.5%)	6 (0.5%)
Infections and infestations	0	0	1 (<0.1%)	0
Liver abscess	0	0	1 (<0.1%)	0
Hepatobiliary disorders	1 (0.3%)	0	2 (0.2%)	2 (0.2%)
Hepatic cyst	0	0	1 (<0.1%)	0
Hepatic mass	1 (0.3%)	0	0	0
Hepatic steatosis	0	0	1 (<0.1%)	1 (<0.1%)
Hepatic cirrhosis	0	0	0	1 (<0.1%)
Investigations	3 (1.0%)	1 (0.3%)	4 (0.3%)	4 (0.3%)
Alanine aminotransferase increased	3 (1.0%)	1 (0.3%)	4 (0.3%)	3 (0.2%)
Liver function test abnormal	2 (0.7%)	0	0	1 (<0.1%)
Aspartate aminotransferase increased	1 (0.3%)	0	0	0

TEAE: treatment-emergent adverse event; SOC: system organ class; PT: preferred term; MedDRA 16.0 n (%): number and percentage of patients with at least one hepatic TEAE, based on SMQ and PT search  
T1DM: Including 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)  
T2DM: Including 6-month main treatment period of EFC11628, EFC11629 and EFC12347

Source: ISS Table 70

The number of hepatic TEAEs in both T1DM and T2DM were small in both treatment groups. In either the T1DM or T2DM pools no patient had an ALT >10 times ULN.

In the T1DM pool, none of the TEAEs reported were serious nor led to treatment discontinuation in the HOE901-U30. In the Lantus group, alanine aminotransferase was increased in 1 patient and led to treatment discontinuation. This patient (012456840139009) had an increase of a screening ALT (1.1 times ULN to 6 times ULN at randomization- day 1).

**Reviewer’s comment: Given the duration of exposure, it is unlikely to be related to exposure to Lantus.**

One patient (012347840270006), with previous history of fatty liver disease, met the definition of Hy’s law in the HOE901-U300 group (with ALT increased to 4.7 times normal and bilirubin increased to 3 times normal) on day 82 of treatment. He was taking medicines that could cause hepatotoxicity including levofloxacin for treatment of a UTI. Patient temporarily discontinued the IMP until normalization of laboratory results. Upon re-challenge with IMP, liver function tests remained normal.

In the T2DM pool, the incidence of hepatic TEAEs was also low and without a clear trend or distribution of events. No hepatic specific TEAEs were identified in the 3-month substudies.

**Reviewer’s comment:**

**The overall number of patients with hepatic impairment in T1DM and T2DM studies is small, and without any clear, clinically meaningful imbalance. The one patient identified as meeting Hy’s law was receiving therapy that was also hepatotoxic and there were no recurrences when re-challenged with HOE901-U300. The distribution of hepatic events in both T1DM and T2DM pools does not reveal a safety signal for HOE901-U300.**

#### Overdose

Events classified as “overdose” with IMP were of particular interest for the clinical reviewer, given that differences in concentration between the two insulins might predispose patients to this event, especially in the beginning of treatment. To fully assess the events classified as overdose, the reviewer went through all narratives provided in the application and identified those classified as “overdose.” Then, the reviewer compared these events with those provided in the datasets. From this comparison, it was noted that there is an occasional discrepancy in the classification of some patients as having “overdosed” with IMP in the narratives, but not classified as such in the dataset. Table 64 displays all the patients that the reviewer found had “overdosed” with IMP; discrepancies are noted in the chart.

The Sponsor defined overdose as the following:

1. *Symptomatic overdose with IMP*- A symptomatic overdose (accidental or intentional) with the IMP is an event suspected by the investigator or spontaneously notified by the patient (not based on systematic insulin consumption check), resulting in clinical

symptoms and/or signs and defined as intake of at least twice the prescribed dose of the IMP per administration.

2. *Symptomatic overdose with NIMP-A* symptomatic overdose (accidental or intentional) with the NIMP is the event suspected by the investigator or spontaneously notified by the patient (not based on systematic pills count of assessment of injection solution consumption, if applicable) and defined as intake of at least twice the prescribed dose of mandatory background. Non-insulin antihyperglycemic therapy (or rescue treatment, if applicable) per administration and resulting in clinical symptoms and/or signs.
3. *Asymptomatic overdose* (accidental or intentional) with the IMP/NIMP is defined as any dose greater than twice the prescribed dose per administration, without clinical symptoms and/or signs, either suspected by the investigator or spontaneously notified by the patient (not based on accountability assessment).

Per the narratives, it is not always clear whether the overdose was due to the IMP vs. NIMP, thus no distinction is made by the reviewer when counting these cases, thus assuming worst-case scenario- that all overdoses are due to IMP. Overall, 6 patients (with and without symptoms) overdosed in the HOE901-U300 group compared to 4 patients in the Lantus group. The onset of overdose occurred earlier in the study for the three patients with T1DM (range of time from 1 to 8 days) compared to patients with T2DM where the first day of overdose ranged from Day 27 to Day 154.

**Table 64 - All patients in Phase2/3 database who overdosed with IMP (symptomatic and asymptomatic)**

			Day of overdose	Intensity	Narrative
Patient	HOE901-U300	Lantus			
011628840075001	1	0	Day 51	mild	Day 51- the patient realized that she accidentally injected her basal insulin (61 units) twice prior evening
011628840036010 <sup>a</sup>	1	0	Day 154	mild	Day 154- intentional overdose (no recorded hypoglycemia) Day 170- intentional overdose (no recorded hypoglycemia)
011628840071003 <sup>a</sup>	1	0	Day 42	mild	Day 42- IMP overdose, no details given
011628840092006 <sup>a</sup>	0	1	Day 84	mild	Day 84- accidental overdose with IMP- no further details provided
011629840523003	0	1	Day 43	moderate	Day 43- patient mistakenly took an additional 60 IU of insulin glargine (Lantus) at his usual dosing time.
011629840018006 <sup>a</sup>	0	1	Day 74	mild	Day 74- accidental asymptomatic overdose
012347124201011	1	0	Day 27	Not recorded	Day27- intentional symptomatic overdose with IMP-injected additional 30 units of IMP in the AM in addition to night's dose of 30 units
012456233106002	1	0	Day 2	No	Day 2-Patient had symptomatic overdose with IMP-no details

			Day of overdose	Intensity	Narrative
<b>Patient</b>	<b>HOE901-U300</b>	<b>Lantus</b>			
					provided.  On Day 5- patient had symptomatic overdose unclear if due to IMP/NIMP
<b>012456348103004</b>	1	0	Day 1	not recorded	Day 1- Patient had overdose, no glucometer reading provided. No details provided Day 137- SAE of hypoglycemia
012456392112003	0	1	Day 8	Not reported	Day 8- patient took 15 units of IMP and “dose of NIMP to the event was 34 units” Day 12- asymptomatic overdose with IMP
<b>Patients with symptomatic overdose are in bold</b>					
<sup>a</sup> There is inconsistent classification of patient (marked in dataset as NOT having an overdose due to IMP vs. narrative state patient had overdose with IMP). Reviewer considered patient to have overdose due to IMP.					

**Reviewer’s comments: Evaluation of the patient narratives revealed a small imbalance in the incidence of patients who overdosed in the HOE901-U300 vs. Lantus group (6 vs. 4 patients respectively). An imbalance was seen in the time in which overdose occurred in the T1DM vs. T2DM populations, with the former having a cluster of overdose within the first 8 days of treatment, while the latter lacked a pattern. Given the small number of patients who overdosed, this difference in time to overdose, may be due to chance.**

A Review performed by Sarah K. Vee, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA), showed that:

Human Factors Study users are able to use the prefilled pen safely and effectively with no reported instances of calculation errors (i.e. multiplying or dividing by 3, resulting in 3-fold over or under doses). However, U-300 will be a new insulin concentration and misunderstanding of the concentration may result in serious harm to the patient, especially in cases of overdose. As a result, DMEPA concludes that proper education and training are provided prior to first injection to ensure that the users are able to safely use this product. The proposed container label, carton, and insert labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

**Reviewer’s comment: I agree with DMEPA’s review, overall, my review, also does not show a clear safety signal due to medication errors. As is emphasized by DMEPA, proper training and education will need to happen for safe use of this product.**

Hyperglycemia during the first week of converting to HOE901-U300

During the review process of this application, there was concern regarding the safety ramifications of the decreased pharmacodynamic effect of HOE901-U300. In particular, there was concern regarding the risk of increased hyperglycemia upon converting from other insulins

(i.e. Lantus) to HOE901-U300. The efficacy data regarding 8-point SMPG and pre-breakfast SMPG suggested that there were increased glucose levels in the HOE901-U300 that peaked~week 2 of three of the four pivotal studies.

The Sponsor answered an information request on November 26, 2014 and clarified that there were 2 reported TEAEs that suggested worsened glycemic control. One report was in the HOE901-U300 group in study EFC11629. This report had an onset of Day 2 of treatment. The patient was considered recovered on Day 9. SMPG levels between Day 2 and Day 8 were above 200 mg/dL (maximum fasting prebreakfast SMPG 288 mg/dL on Day 5, maximum random SMPG 449 mg/dL on Day 9). The patient prematurely discontinued the study Day 9 due to “poor protocol compliance.” The second reported TEAE was in the Lantus group. “Hyperglycemia” was reported on Day 3 (no plasma glucose provided, with recovery within 30 min without corrective treatment).

**Reviewer’s comments: Despite the increased pre-breakfast SMPG and 8-point glucose readings noted across studies, in section 6 Review of Efficacy, these two cases of hyperglycemia(1 in HOE901-U300 and 1 in Lantus) do not suggest that this glycemic difference is clinically significant.**

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The reviewer has suggested tables for common adverse events in T1DM (Table 65) and T2DM (Table 66) safety population. . These tables show the TEAEs occurring in  $\geq 5\%$  in either treatment group by preferred term.

Based on this grouping, there are a greater percentage of patients who experienced TEAEs in the HOE901-U300 arm compared to the Lantus arm for “nasopharyngitis” and “upper respiratory tract infection” in both T1DM and T2DM.

**Table 65 - TEAEs occurring in  $\geq 5\%$  of T1DM patients in HOE901-U300 and Lantus groups, arranged by Preferred term, during the on-treatment 6 month period (T1DM safety population)**

	<b>HOE901-U300 % (n=304)</b>	<b>LANTUS, % (n=304)</b>
Nasopharyngitis	12.8	10.9
Upper respiratory tract infection	9.5	7.6

**Table 66 – TEAEs occurring in  $\geq 5\%$  of a pool of T2DM patients in HOE901-U300 and Lantus groups, arranged by Preferred term, during the on-treatment 6 month period (T2DM safety population)**

	<b>TOUJEO, % (n=1,242)</b>	<b>LANTUS, % (n=1,246)</b>
Nasopharyngitis	7.1	5.8
Upper respiratory tract infection	5.7	5.4

**Reviewer’s comments:**

**The significance of the small imbalance of nasopharyngitis between insulins is unclear. This reviewer considers that this imbalance is probably due to chance. The imbalance in the other categories is also likely due to chance.**

T1DM

See Table 67 for incidence comparisons of common TEAEs with HLTs  $\geq 2\%$  in any treatment group. Most of the TEAEs reported were under infections and infestations (HOE901-U300: 39.8% vs Lantus 36.8%). This difference was driven by the HLT of upper respiratory tract infections and viral infections NEC, both HLTs that were higher in the HOE901-U300 group. The events from these HLTs were not considered serious TEAEs and none led to treatment discontinuation.

Note that the sponsor’s calculations of ‘risk differences’ in Tables 69 and 70 should be considered exploratory as the study was not powered to assess these endpoints.

**Table 67 – Risk difference (95% CI) of common TEAE (s) by primary SOC, HLT and PT during the main on-treatment period: T1DM study pools – Safety population**

Primary System Organ Class HLT: High Level Term Preferred Term n (%)	HOE901-U300 (N=304)	Lantus (N=304)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
Any class	191 (62.8%)	179 (58.9%)	3.9%	(-3.82% to 11.63%)
<b>INFECTIONS AND INFESTATIONS</b>	<b>121 (39.8%)</b>	<b>112 (36.8%)</b>	<b>2.9%</b>	<b>(-4.78% to 10.62%)</b>
HLT: Abdominal and gastrointestinal infections	5 (1.6%)	8 (2.6%)	-0.9%	(-3.37% to 1.40%)
Gastroenteritis	5 (1.6%)	8 (2.6%)	-0.9%	(-3.37% to 1.40%)
HLT: Influenza viral infections	10 (3.3%)	13 (4.3%)	-1.0%	(-4.03% to 2.02%)
Avian influenza	0	1 (0.3%)		
Influenza	10 (3.3%)	12 (3.9%)	-0.6%	(-3.63% to 2.28%)
HLT: Lower respiratory tract and lung infections	7 (2.3%)	9 (3.0%)	-0.6%	(-3.27% to 1.94%)
Bronchitis	6 (2.0%)	6 (2.0%)	0.0%	(-2.29% to 2.30%)
Lower respiratory tract infection	0	3 (1.0%)	-0.9%	(-2.42% to 0.45%)
Pneumonia	1 (0.3%)	1 (0.3%)		
HLT: Streptococcal infections	5 (1.6%)	7 (2.3%)	-0.6%	(-2.95% to 1.64%)
Erysipelas	2 (0.7%)	1 (0.3%)	0.3%	(-0.95% to 1.62%)
Pharyngitis streptococcal	3 (1.0%)	5 (1.6%)	-0.6%	(-2.57% to 1.25%)
Streptococcal infection	0	1 (0.3%)		
HLT: Upper respiratory tract infections	78 (25.7%)	66 (21.7%)	3.9%	(-2.81% to 10.67%)
Acute sinusitis	1 (0.3%)	2 (0.7%)	-0.3%	(-1.61% to 0.96%)
Chronic tonsillitis	0	1 (0.3%)		
Laryngitis	1 (0.3%)	0		
Nasopharyngitis	39 (12.8%)	33 (10.9%)	1.9%	(-3.16% to 7.00%)
Peritonsillar abscess	0	1 (0.3%)		
Pharyngitis	1 (0.3%)	3 (1.0%)	-0.6%	(-2.09% to 0.78%)
Rhinitis	2 (0.7%)	0	0.6%	(-0.62% to 1.92%)
Sinusitis	9 (3.0%)	5 (1.6%)	1.3%	(-1.14% to 3.78%)
Tonsillitis	1 (0.3%)	0		
Upper respiratory tract infection	29 (9.5%)	23 (7.6%)	1.9%	(-2.44% to 6.43%)
HLT: Viral infections NEC	18 (5.9%)	7 (2.3%)	3.6%	(0.48% to 6.77%)
Ear infection viral	0	1 (0.3%)		
Gastroenteritis viral	3 (1.0%)	2 (0.7%)	0.3%	(-1.11% to 1.75%)
Gastrointestinal viral infection	4 (1.3%)	0	1.3%	(-0.25% to 2.89%)
Respiratory tract infection viral	2 (0.7%)	1 (0.3%)	0.3%	(-0.95% to 1.62%)
Viral infection	5 (1.6%)	1 (0.3%)	1.3%	(-0.37% to 3.01%)
Viral pharyngitis	2 (0.7%)	0	0.6%	(-0.63% to 1.94%)
Viral upper respiratory tract infection	2 (0.7%)	2 (0.7%)	0.0%	(-1.43% to 1.44%)

Primary System Organ Class HLT: High Level Term Preferred Term n (%)	HOE901-U300 (N=304)	Lantus (N=304)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
<b>METABOLISM AND NUTRITION DISORDERS</b>	14 (4.6%)	16 (5.3%)	-0.6%	(-4.14% to 2.85%)
HLT: Hypoglycaemic conditions NEC	9 (3.0%)	12 (3.9%)	-0.9%	(-3.94% to 1.99%)
Hypoglycaemia	9 (3.0%)	12 (3.9%)	-0.9%	(-3.94% to 1.99%)
<b>NERVOUS SYSTEM DISORDERS</b>	29 (9.5%)	25 (8.2%)	1.2%	(-3.21% to 5.76%)
HLT: Headaches NEC	15 (4.9%)	14 (4.6%)	0.3%	(-3.07% to 3.67%)
Headache	14 (4.6%)	14 (4.6%)	0.0%	(-3.34% to 3.30%)
Sinus headache	1 (0.3%)	0		
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	21 (6.9%)	21 (6.9%)	0.0%	(-4.00% to 3.89%)
HLT: Upper respiratory tract signs and symptoms	5 (1.6%)	9 (3.0%)	-1.3%	(-3.69% to 1.02%)
Oropharyngeal pain	4 (1.3%)	7 (2.3%)	-1.0%	(-3.11% to 1.11%)
Rhinorrhoea	2 (0.7%)	1 (0.3%)	0.3%	(-1.11% to 1.76%)
Sneezing	1 (0.3%)	0		
Throat irritation	0	1 (0.3%)		
Upper respiratory tract inflammation	1 (0.3%)	0		
<b>GASTROINTESTINAL DISORDERS</b>	35 (11.5%)	36 (11.8%)	-0.3%	(-5.43% to 4.70%)
HLT: Diarrhoea (excl infective)	7 (2.3%)	6 (2.0%)	0.3%	(-1.96% to 2.59%)
Diarrhoea	7 (2.3%)	6 (2.0%)	0.3%	(-1.96% to 2.59%)
HLT: Nausea and vomiting symptoms	11 (3.6%)	14 (4.6%)	-1.0%	(-4.15% to 2.15%)
Nausea	8 (2.6%)	5 (1.6%)	0.9%	(-1.31% to 3.27%)
Vomiting	5 (1.6%)	12 (3.9%)	-2.3%	(-4.99% to 0.37%)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	26 (8.6%)	29 (9.5%)	-0.9%	(-5.54% to 3.58%)
HLT: Musculoskeletal and connective tissue pain and discomfort	13 (4.3%)	13 (4.3%)	0.0%	(-3.21% to 3.22%)
Back pain	9 (3.0%)	7 (2.3%)	0.6%	(-1.89% to 3.20%)
Flank pain	2 (0.7%)	0	0.6%	(-0.62% to 1.92%)
Musculoskeletal pain	1 (0.3%)	3 (1.0%)	-0.6%	(-2.09% to 0.78%)
Neck pain	1 (0.3%)	2 (0.7%)	-0.3%	(-1.61% to 0.96%)
Pain in extremity	3 (1.0%)	3 (1.0%)	0.0%	(-1.69% to 1.70%)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	35 (11.5%)	25 (8.2%)	3.2%	(-1.38% to 7.83%)
HLT: Asthenic conditions	11 (3.6%)	10 (3.3%)	0.3%	(-2.58% to 3.22%)
Asthenia	1 (0.3%)	1 (0.3%)		
Fatigue	7 (2.3%)	7 (2.3%)	0.0%	(-2.39% to 2.36%)

Primary System Organ Class HLT: High Level Term Preferred Term n (%)	HOE901-U300 (N=304)	Lantus (N=304)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
Malaise	4 (1.3%)	2 (0.7%)	0.6%	(-1.03% to 2.34%)
HLT: Injection site reactions	8 (2.6%)	5 (1.6%)	0.9%	(-1.31% to 3.27%)
Injection site bruising	5 (1.6%)	2 (0.7%)	0.9%	(-0.82% to 2.79%)
Injection site discomfort	0	1 (0.3%)		
Injection site erythema	0	1 (0.3%)		
Injection site oedema	1 (0.3%)	0		
Injection site pain	3 (1.0%)	1 (0.3%)	0.6%	(-0.77% to 2.08%)
Injection site swelling	0	1 (0.3%)		
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>				
HLT: Skin injuries NEC	22 (7.2%)	23 (7.6%)	-0.3%	(-4.49% to 3.83%)
Confusion	6 (2.0%)	8 (2.6%)	-0.6%	(-3.12% to 1.80%)
Excoriations	2 (0.7%)	4 (1.3%)	-0.6%	(-2.35% to 1.04%)
Lacerations	1 (0.3%)	2 (0.7%)	-0.3%	(-1.61% to 0.96%)
Scratches	2 (0.7%)	2 (0.7%)	0.0%	(-1.43% to 1.42%)
Scratch	1 (0.3%)	0		

TEAE: treatment-emergent adverse event; SOC: system organ class; HLT: high level term; PT: preferred term; MedDRA 16.0

n (%): number and percentage of patients with at least one TEAE; Risk difference: HOE901-U300 risk – Lantus risk

Common TEAEs: HLTs  $\geq$  2% in any treatment group

Studies included: 6-month main treatment period of EFC12456 and 16-week treatment period of PDY12777, all dosing regimens (morning or evening injection)

<sup>a</sup> Based on a fixed-effect meta-analysis using Cochran-Mantel-Haenszel method. Risk difference and 95% CI not provided for PTs < 0.5% in both treatment groups

Note: Table sorted by SOC internationally agreed order and alphabetic order of HLT and PT

Source: ISS Table 57

Overall, the findings in Table 67 are supportive of the results presented in the grouped T1DM and T2DM pool in Table 65.

## T2DM

See Table 68 for incidence comparisons of common TEAEs with HLTs  $\geq$  2% in any treatment group. Similar to the T1DM, in the T2DM pool, most of the TEAEs reported were under infections and infestations (HOE901-U300: 30.7% vs Lantus 30.5%). This difference was driven by the HLT of upper respiratory tract infections, which was slightly higher in the HOE901-U300 vs. Lantus group (16.2% vs. 15.3% respectively). Among common TEAEs, HLT terms with a difference of  $\geq$  1% in the HOE901-U300 were in “headaches NEC.” None of the events from this HLT was serious or led to treatment discontinuation.

**Table 68 - Risk difference (95% CI) of common TEAE (s) by primary SOC, HLT and PT during the main on-treatment period: T2DM study pools – safety population**

Primary System Organ Class	HLT: High Level Term Preferred Term n (%)	HOE901-U300 (N=1242)	Lantus (N=1246)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
Any class		712 (57.3%)	669 (53.7%)	3.6%	(-0.26% to 7.54%)
<b>INFECTIONS AND INFESTATIONS</b>		381 (30.7%)	380 (30.5%)	0.1%	(-3.44% to 3.80%)
HLT: Influenza viral infections					
Influenza	30 (2.4%)	30 (2.4%)	33 (2.6%)	-0.2%	(-1.47% to 1.00%)
HLT: Lower respiratory tract and lung infections					
Bronchitis	49 (3.9%)	41 (3.3%)	56 (4.5%)	-0.5%	(-2.13% to 1.02%)
Bronchopneumonia	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)		
Lower respiratory tract infection	1 (<0.1%)	1 (<0.1%)	3 (0.2%)		
Lung infection	0	0	1 (<0.1%)		
Pneumonia	6 (0.5%)	6 (0.5%)	9 (0.7%)	-0.2%	(-0.85% to 0.37%)
HLT: Upper respiratory tract infections					
Acute sinusitis	201 (16.2%)	4 (0.3%)	191 (15.3%)	0.8%	(-2.00% to 3.72%)
Acute tonsillitis	1 (<0.1%)	1 (<0.1%)	2 (0.2%)	-0.3%	(-0.89% to 0.25%)
Chronic sinusitis	2 (0.2%)	2 (0.2%)	0		
Chronic tonsillitis	1 (<0.1%)	1 (<0.1%)	0		
Laryngitis	1 (<0.1%)	1 (<0.1%)	4 (0.3%)		
Nasopharyngitis	88 (7.1%)	88 (7.1%)	72 (5.8%)	1.3%	(-0.61% to 3.24%)
Pharyngitis	10 (0.8%)	10 (0.8%)	15 (1.2%)	-0.4%	(-1.18% to 0.38%)
Pharyngotonsillitis	0	0	2 (0.2%)		
Rhinitis	2 (0.2%)	2 (0.2%)	0		
Sinusitis	26 (2.1%)	26 (2.1%)	31 (2.5%)	-0.4%	(-1.57% to 0.78%)
Tonsillitis	2 (0.2%)	2 (0.2%)	0		
Tracheitis	1 (<0.1%)	1 (<0.1%)	0		
Tracheobronchitis	0	0	1 (<0.1%)		
Upper respiratory tract infection	71 (5.7%)	71 (5.7%)	67 (5.4%)	0.3%	(-1.46% to 2.14%)
HLT: Urinary tract infections					
Cystitis	35 (2.8%)	5 (0.4%)	32 (2.6%)	0.2%	(-1.02% to 1.52%)
Kidney infection	0	0	1 (<0.1%)		
Pyelonephritis	0	0	1 (<0.1%)		
Pyelonephritis acute	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)		
Pyelonephritis chronic	0	0	1 (<0.1%)		
Urinary tract infection	29 (2.3%)	29 (2.3%)	24 (1.9%)	0.4%	(-0.72% to 1.54%)

Primary System Organ Class HLT: High Level Term Preferred Term n (%)	HOE901-U300 (N=1242)	Lantus (N=1246)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
HLT: Viral infections NEC	43 (3.5%)	40 (3.2%)	0.2%	(-1.16% to 1.66%)
Bronchitis viral	1 (<0.1%)	0		
Conjunctivitis viral	1 (<0.1%)	0		
Gastroenteritis viral	22 (1.8%)	13 (1.0%)	0.7%	(-0.20% to 1.65%)
Gastrointestinal viral infection	0	4 (0.3%)		
Pneumonia viral	0	1 (<0.1%)		
Respiratory tract infection viral	4 (0.3%)	7 (0.6%)	-0.2%	(-0.78% to 0.30%)
Viral infection	5 (0.4%)	8 (0.6%)	-0.2%	(-0.83% to 0.35%)
Viral pharyngitis	1 (<0.1%)	0		
Viral rhinitis	0	2 (0.2%)		
Viral upper respiratory tract infection	11 (0.9%)	6 (0.5%)	0.4%	(-0.24% to 1.05%)
<b>NERVOUS SYSTEM DISORDERS</b>	160 (12.9%)	119 (9.6%)	3.3%	(0.86% to 5.81%)
HLT: Headaches NEC	65 (5.2%)	48 (3.9%)	1.3%	(-0.25% to 3.02%)
Headache	61 (4.9%)	47 (3.8%)	1.1%	(-0.45% to 2.74%)
Sinus headache	5 (0.4%)	3 (0.2%)		
Tension headache	1 (<0.1%)	0		
HLT: Neurological signs and symptoms NEC	26 (2.1%)	21 (1.7%)	0.4%	(-0.66% to 1.48%)
Cerebrospinal fluid leakage	1 (<0.1%)	0		
Dizziness	20 (1.6%)	19 (1.5%)	0.0%	(-0.89% to 1.06%)
Dizziness exertional	1 (<0.1%)	0		
Dizziness postural	3 (0.2%)	1 (<0.1%)		
Presyncope	1 (<0.1%)	1 (<0.1%)		
<b>VASCULAR DISORDERS</b>	43 (3.5%)	44 (3.5%)	0.0%	(-1.51% to 1.37%)
HLT: Vascular hypertensive disorders NEC	29 (2.3%)	27 (2.2%)	0.1%	(-1.00% to 1.33%)
Essential hypertension	0	3 (0.2%)		
Hypertension	29 (2.3%)	24 (1.9%)	0.4%	(-0.73% to 1.54%)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	89 (7.2%)	81 (6.5%)	0.6%	(-1.32% to 2.64%)
HLT: Coughing and associated symptoms	21 (1.7%)	25 (2.0%)	-0.3%	(-1.37% to 0.74%)
Allergic cough	1 (<0.1%)	0		
Cough	19 (1.5%)	25 (2.0%)	-0.4%	(-1.51% to 0.56%)

Primary System Organ Class	HOE901-U300 (N=1242)	Lantus (N=1246)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
<b>HLT: High Level Term</b>				
<b>Preferred Term n (%)</b>				
Productive cough	1 (<0.1%)	0		
<b>HLT: Upper respiratory tract signs and symptoms</b>	27 (2.2%)	17 (1.4%)	0.8%	(-0.23% to 1.84%)
Dry throat	1 (<0.1%)	0		
Dysphonia	1 (<0.1%)	0		
Nasal discomfort	0	1 (<0.1%)		
Oropharyngeal pain	16 (1.3%)	12 (1.0%)	0.3%	(-0.50% to 1.15%)
Rhinorrhoea	7 (0.6%)	3 (0.2%)	0.3%	(-0.17% to 0.82%)
Sneezing	2 (0.2%)	0		
Throat irritation	1 (<0.1%)	2 (0.2%)		
Upper respiratory tract congestion	1 (<0.1%)	0		
Upper respiratory tract inflammation	1 (<0.1%)	0		
<b>GASTROINTESTINAL DISORDERS</b>	161 (13.0%)	144 (11.6%)	1.4%	(-1.17% to 3.98%)
<b>HLT: Diarrhoea (excl infective)</b>	47 (3.8%)	38 (3.0%)	0.7%	(-0.69% to 2.16%)
Diarrhoea	47 (3.8%)	38 (3.0%)	0.7%	(-0.69% to 2.16%)
<b>HLT: Nausea and vomiting symptoms</b>	54 (4.3%)	45 (3.6%)	0.7%	(-0.80% to 2.27%)
Nausea	40 (3.2%)	27 (2.2%)	1.0%	(-0.22% to 2.32%)
Vomiting	21 (1.7%)	24 (1.9%)	-0.2%	(-1.28% to 0.81%)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	155 (12.5%)	164 (13.2%)	-0.6%	(-3.31% to 1.93%)
<b>HLT: Joint related signs and symptoms</b>	30 (2.4%)	36 (2.9%)	-0.4%	(-1.74% to 0.78%)
Arthralgia	26 (2.1%)	33 (2.6%)	-0.5%	(-1.75% to 0.64%)
Joint effusion	0	1 (<0.1%)		
Joint range of motion decreased	0	1 (<0.1%)		
Joint swelling	5 (0.4%)	1 (<0.1%)		
<b>HLT: Musculoskeletal and connective tissue pain and discomfort</b>	69 (5.6%)	74 (5.9%)	-0.3%	(-2.21% to 1.44%)
Back pain	30 (2.4%)	37 (3.0%)	-0.5%	(-1.83% to 0.72%)
Flank pain	2 (0.2%)	1 (<0.1%)		
Musculoskeletal chest pain	4 (0.3%)	4 (0.3%)		
Musculoskeletal discomfort	0	1 (<0.1%)		

Primary System Organ Class HLT: High Level Term Preferred Term n (%)	HOE901-U300 (N=1242)	Lantus (N=1246)	Risk difference <sup>a</sup>	95% CI <sup>a</sup>
Musculoskeletal pain	14 (1.1%)	13 (1.0%)	0.0%	(-0.73% to 0.90%)
Neck pain	10 (0.8%)	7 (0.6%)	0.2%	(-0.42% to 0.91%)
Pain in extremity	19 (1.5%)	19 (1.5%)	0.0%	(-0.96% to 0.97%)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>124 (10.0%)</b>	<b>112 (9.0%)</b>	<b>0.9%</b>	<b>(-1.30% to 3.29%)</b>
HLT: Asthenic conditions	33 (2.7%)	26 (2.1%)	0.5%	(-0.63% to 1.76%)
Asthenia	5 (0.4%)	4 (0.3%)		
Fatigue	26 (2.1%)	20 (1.6%)	0.4%	(-0.57% to 1.54%)
Malaise	3 (0.2%)	2 (0.2%)		
HLT: Injection site reactions	30 (2.4%)	38 (3.0%)	-0.6%	(-1.91% to 0.65%)
Injection site atrophy	0	1 (<0.1%)		
Injection site bruising	9 (0.7%)	12 (1.0%)	-0.2%	(-0.97% to 0.50%)
Injection site discomfort	1 (<0.1%)	0		
Injection site erythema	1 (<0.1%)	6 (0.5%)		
Injection site haematoma	1 (<0.1%)	0		
Injection site haemorrhage	3 (0.2%)	7 (0.6%)	-0.3%	(-0.86% to 0.22%)
Injection site induration	0	4 (0.3%)		
Injection site inflammation	1 (<0.1%)	0		
Injection site irritation	1 (<0.1%)	1 (<0.1%)		
Injection site pain	10 (0.8%)	13 (1.0%)	-0.2%	(-1.00% to 0.53%)
Injection site pruritus	4 (0.3%)	0		
Injection site rash	0	1 (<0.1%)		
Injection site reaction	4 (0.3%)	2 (0.2%)		
Injection site swelling	0	1 (<0.1%)		
HLT: Oedema NEC	35 (2.8%)	36 (2.9%)	0.0%	(-1.38% to 1.23%)
Generalised oedema	1 (<0.1%)	0		
Oedema	1 (<0.1%)	0		
Oedema peripheral	34 (2.7%)	36 (2.9%)	-0.1%	(-1.45% to 1.14%)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>98 (7.9%)</b>	<b>79 (6.3%)</b>	<b>1.5%</b>	<b>(-0.47% to 3.57%)</b>
HLT: Muscle, tendon and ligament injuries	25 (2.0%)	18 (1.4%)	0.5%	(-0.46% to 1.59%)
Epicondylitis	0	3 (0.2%)		
Ligament rupture	1 (<0.1%)	0		
Ligament sprain	12 (1.0%)	4 (0.3%)	0.6%	(-0.00% to 1.29%)
Muscle strain	9 (0.7%)	5 (0.4%)	0.3%	(-0.27% to 0.91%)

Source: ISS, Table 58

Results of the 3-month administration substudies were similar to those presented in the T2DM population above.

**Reviewer’s comments: The separate analysis of common adverse events in the T1DM and T2DM safety pools are consistent with the results when these two populations were grouped together. Overall, there does not appear to be a clear safety signal in HOE901-U300 in the listing of common adverse events.**

#### 7.4.2 Laboratory Findings

Potentially clinically significant abnormality (PCSA) values were defined as “abnormal values” and considered medically important according to predefined criteria/thresholds (documented in PCSA version dated January 2009, see 5.3.5.3 Ph2/3 SAP-Safety). This reviewer agrees with the criteria for potentially clinically significant abnormalities used by the Sponsor (criteria are not listed in this review). All post-baseline laboratory parameters were analyzed in a central laboratory. The Sponsor’s analyzed parameters are listed in Table 69.

**Table 69 – Summary of post-baseline data collected for laboratory, vital signs, EKG and immunogenicity in the Phase 2/3 program**

Parameter	Post-baseline data collected
Laboratory variables in each	<p>The following clinical laboratory data were collected and forwarded to a central laboratory</p> <p>Phase 2/3 study:</p> <ul style="list-style-type: none"> <li>• Hematology <ul style="list-style-type: none"> <li>- Red blood cells (RBCs) and platelets including hemoglobin, hematocrit, RBC count, and platelet count</li> <li>- White blood cells (WBCs) including WBC count and differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils)</li> </ul> </li> <li>• Clinical chemistry <ul style="list-style-type: none"> <li>- Serum lipids including total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (serum lipids were not collected in study PDY12777)</li> <li>- Electrolytes including sodium, potassium, calcium, and chloride (calcium and chloride not collected in studies EFC12347, EFC12456, and PDY12777)</li> <li>- Renal function including creatinine, creatinine clearance (Cockcroft-Gault formula), estimated glomerular filtration rate (eGFR) (modified diet and renal disease [MDRD] formula) and uric acid (uric acid was not collected in studies EFC12347, EFC12456, and PDY12777)</li> <li>- Liver function including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin</li> </ul> </li> </ul>
Vital signs	Sitting systolic blood pressure (SBP, mmHg), sitting diastolic blood pressure (DBP, mmHg), sitting heart rate (HR, beat per minute [bpm]), and body weight (kg).

ECG For all Phase 2/3 studies, only ECG status (normal/abnormal, and clinical significance in case of abnormality) was collected and is described in the individual CSRs.

Anti- insulin antibodies  
(Immunogenicity)

For all Phase 2/3 studies except PDY12777, AIA assessments were performed at a centralized laboratory using a validated AIA binding assay methodology.

Anti-insulin antibody status (positive/negative), AIA titers, and cross-reactivity to human insulin have been evaluated. The timing of immunogenicity assessments during the main 6-month on-treatment period was similar across studies (baseline [as defined in 5.3.5.3 Ph2/3 SAP-Safety, Week 4, Week 12 and Week 26 [Month 6]

At the time of the data cut-off date, AIA samples of the main 6-month on-treatment period were analyzed for study EFC12456 in T1DM and studies EFC11628 and EFC11629 in T2DM.

Source: ISS, Table 8

#### Hematology:

In both T1DM and T2DM, there were no clinically relevant changes based on analyses of central tendency (i.e. means values) observed for hemoglobin, hematocrit, RBC, platelets or WBC over time, compared to baseline values in both treatment groups. The hematological categories were mostly balanced between treatment groups (data not shown). Three patients randomized to ? discontinued the study due to adverse events related to hematological abnormalities. Per review of the narratives, there is no convincing evidence that the hematological abnormalities in these patients were due to the investigational drug.

#### Electrolytes and Lipids:

No imbalances in measures of electrolytes and lipids between treatment groups based on analyses of central tendency were observed in both T1DM and T2DM populations. There were no abnormalities categorized as a serious TEAE or a TEAE leading to treatment discontinuation in neither T1DM nor T2DM population.

#### Renal function

No treatment group imbalances of clinically relevant changes in measures of renal function based on analyses of central tendency were observed between treatment groups (eGFR, creatinine, estimated creatinine clearance, and uric acid) in either T1DM or T2DM.

In the T1DM group, there were 3 patients with TEAEs suggesting abnormal renal function (PT terms: “acute renal failure” and “blood creatinine increased”). Two of these patients were in the HOE901-U300 group and 1 in the Lantus group. None of the TEAEs reported were severe or serious and none led to treatment discontinuation.

In the T2DM pool, there were 6 patients with TEAEs suggesting abnormal renal function (PT terms: “creatinine renal clearance decrease,” “blood creatinine increased,” “glomerular filtration

rate decreased”). Two of these patients were in the HOE901-U300 group and 4 in the Lantus group. Of these patients, one patient in the Lantus group, discontinued treatment due to TEAE.

#### Liver function tests

Refer to 7.3.5 Submission Specific Primary Safety Concerns, section discussing hepatic events.

#### **Reviewer’s comments:**

**Overall there are no evident safety signals based on results of routine laboratory testing between HOE901-U300 and Lantus.**

#### **7.4.3 Vital Signs**

In the Phase 2/3 T1DM pool, the percentage of patients with at least 1 post baseline clinical significant abnormal value for SBP, DBP, and HR was small and similar in both groups (data not shown). In both treatment groups, there were no relevant changes in mean blood pressure (systolic and diastolic) and HR from baseline to Month 6, and there were no important differences between treatment groups.

In the T1DM pool, the mean (SD) change in weight from baseline to the last on-treatment value was 0.46 (3.15) kg in the HOE901-U300 group and 1.02 (3.08) kg in the Lantus group. In the T2DM pool, the mean (SD) change in weight from baseline to the last on-treatment value was 0.52 (3.51) kg in the HOE901-U300 group and 0.79 (3.23) kg in the Lantus group.

#### **Reviewer’s comments:**

**There was no safety signal for HOE901-U300 in regards to vital signs. At the conclusion of the trials, there was less weight gain in the HOE901-U300 group in both the T1DM and T2DM pools compared to the Lantus group.**

#### **7.4.4 Electrocardiograms (ECGs)**

Investigator read ECGs at pre-defined visit. Overall, the number of abnormal clinically important ECG readings, post baseline, was similar between HOE901-U300 group in both T1DM and T2DM patients. Study EFC12347 had a greater number of patients with post baseline clinically important ECG; however this included 6 patients who at baseline had abnormal ECGs.

#### **Reviewer’s comments:**

**There is no imbalance in ECG showing clinically significant abnormalities between HOE901-U300 and Lantus.**

#### **7.4.5 Special Safety Studies/Clinical Trials**

[Redacted content]

(b) (4)

All eligible patients first randomized to and treated with HOE901-U300 in the main study and who completed the 6-month on-treatment period (Visit 10) was asked to participate in the 3-month substudy. These patients were eligible for a second randomization process either to continue fixed time dosing (every 24 hours) or to inject HOE901-U300 once daily in the evening at intervals of  $24 \pm 3$  hours at least 2 days a week. A second informed consent was obtained prior to any substudy procedures.

The dosing times will be referred to as follows:

- **fixed dosing** -- dosing every 24 hours
- **adaptable dosing** -- dosing at intervals of  $24 \pm 3$  hours at least 2 days a week
- **reference dosing time** -- dosing time established at the beginning of the 6-month treatment period

In both substudies, there was a shift in the reference dosing time, with a stable time interval between 2 injections.

A key component in the evaluation of these trials was the compliance to dosing interval regimen (that is, fixed dosing or adaptable dosing). Although the initial dosing time was set at the beginning of the main EFC11628 6-month treatment period, some patients shifted their reference dosing time by 1 or 2 hours, hence establishing a “new” reference dosing time. Because of this shift in reference dosing time, the Sponsor analyzed both time periods:

- 1) the average time interval between 2 consecutive injections
- 2) The time interval between injections and reference injection time

Statistical considerations in regards to compliance included compliance to treatment and compliance to dosing interval regimen. Compliance to one daily injections (treatment) was the number of days with at least 1 administration of HOE901-U300 compared to the planned days with HOE901-U300 administration substudy. Compliance to dosing interval regimen (either fixed or adaptable) was calculated using injection times documented during the last 7 days before Visit 10.1 and the last 7 days before Visit 11 (see Figure 37). Neither substudy had a pre-specified power calculation for the primary endpoint. There was also no multiplicity adjustment to minimize Type 1 error.

Overall, the design and statistics used in EFC11628 substudy and EFC11629 substudy were similar, as shown by Table 70.

**Table 70 - Characteristics of EFC11628 and EFC11629 substudies**

	EFC11628 Substudy	EFC11629 substudy
	<b>DESIGN</b>	
Primary objective	<b>compare the efficacy</b> of HOE901-U300 injected <b>once daily every 24 hrs.</b> vs. HOE901-U300 <b>once daily at intervals of <math>24 \pm 3</math> hours</b> in terms of: <ul style="list-style-type: none"> <li>- change of HbA1c from Month 6 (main study endpoint) to Month 9 (main study extension period) in patients with T2DM.</li> </ul>	
Secondary objective	compare the safety (in particular hypoglycemia) of the 2 injection regimens of HOE901-U300	

Efficacy measures and variables ( <i>in italics</i> )	<ol style="list-style-type: none"> <li>1. HbA1c (<i>change from substudy baseline [Month 6] to endpoint [Month 9]</i>)</li> <li>2. FPG <i>-change FPG(from Month 6 to Month 9)</i></li> <li>3. pre-injection SMPG <i>-change in pre-injection SMP (mean over last 7 days from Month 6 to Month 9)</i> <i>-change in variability of pre-injection SMPG</i></li> <li>4. 8-point glucose profiles <i>-change in 8-point SMPG per time point from Month 6 to Month 9</i></li> </ol> <p><i>Other non- efficacy variables:</i></p> <ul style="list-style-type: none"> <li>- <i>change in daily basal insulin dose (U and U/kg body weight) from baseline (Month 6) to (Month 9)</i> <i>**Specific to substudy EFC11628-Change in total (basal plus mealtime) daily insulin dose (U and U/kg body weight) from (Month 6) to (Month 9)</i></li> </ul>		
Safety variables	<ul style="list-style-type: none"> <li>• all hypoglycemia events including nocturnal hypoglycemia events</li> <li>• injection site reactions and hypersensitivity reactions</li> <li>• adverse events of special interest (AESIs) with immediate notification: <ul style="list-style-type: none"> <li>- ALT increase, pregnancy, symptomatic overdose with IMP/NIMP</li> </ul> </li> <li>• AESIs without immediate notification: <ul style="list-style-type: none"> <li>- asymptomatic overdose with IMP/NIMP</li> </ul> </li> <li>• other AEs or SAEs;</li> <li>• Other safety information including blood pressure, heart rate, and weight.</li> </ul>		
Safety laboratory measures	<p>hematology, clinical chemistry, lipids, serum pregnancy test in women of child bearing potential</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">glutamic acid decarboxylase antibodies</td> <td style="width: 50%;">anti-insulin antibody</td> </tr> </table>	glutamic acid decarboxylase antibodies	anti-insulin antibody
glutamic acid decarboxylase antibodies	anti-insulin antibody		
Duration of study	3 months: Month 6 (visit10) to Month 9 (visit 11)		
Eligible patients	Optional for patients randomized and treated with HOE901-U300 and completed the preceding main 6-month on-treatment period		
Randomization	1:1 randomization to : HOE901-U300 every 24 hours (fixed) <b>or</b> HOE 901-U300 daily 24 ± 3 hours than fixed schedule (adaptable dosing intervals)		
Differences in trial design for substudy participants compared to those who did not participate	<ul style="list-style-type: none"> <li>-different dosing intervals of HOE901-U300</li> <li>-separate informed consent</li> <li>-2 additional phone calls after randomization in the substudy</li> <li>-additional mandatory SMPG measurements before additional phone calls</li> </ul>		
Blinding	The clinical team was blinded to the treatment regimen.		
Inclusion criteria in addition to the main study's criteria	<ul style="list-style-type: none"> <li>-Completion of the main 6-month on-treatment period (Visit 10).</li> <li>-Randomized and treated with HOE901-U300 during the main 6-month on-treatment period</li> <li>-Signed written substudy informed consent.</li> </ul>		
Exclusion criteria in addition to the main study's criteria	<ul style="list-style-type: none"> <li>-Patient not willing to use the adaptable injection intervals of 24 ± 3 hours on at least 2 days a week.</li> <li>-In the Investigator's opinion, not able to comply with an adaptable dosing intervals schedule.</li> <li>-Health condition which precludes safe continuation of participation in the study.</li> </ul>		
Treatment discontinuation during substudy period	<p>by <b>Investigator</b> for:</p> <ul style="list-style-type: none"> <li>-suspected adverse drug reaction</li> <li>-intercurrent condition</li> <li>-basal insulin dose needed to be decreased below 39 U/day</li> </ul>		

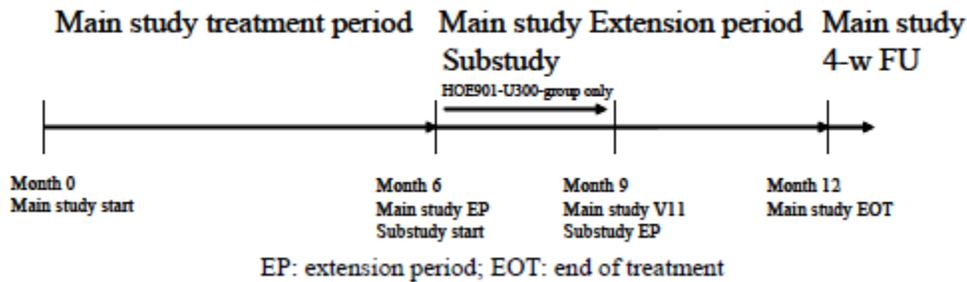
	-request of sponsor *In case of permanent discontinuation the patients were assessed planned for last day of dosing and for safety follow up. Ongoing AEs were to be followed until patient recovered or AE stabilized.	
Non-investigational medicinal products approved (NIMP)	-mealtime (bolus) insulin -metformin	- Patients were to continue their stable dose of OAD therapy (started in main study period). - No other concomitant antidiabetic treatments were to be used. -Short term use (i.e., 10 days at maximum) of short-acting insulin therapy (e.g., due to acute illness or surgery) was not considered as rescue therapy.
Titration of IMP and NIMP	IMP- per section: <b>Common elements among 4 pivotal studies</b> NIMP: <b>bolus insulin-</b> per investigator <b>metformin-</b> kept stable, unless safety concern	IMP- per section: <b>Common elements among 4 pivotal studies</b>  NIMP- doses were to be kept stable unless need of rescue or safety concern.
Site of IMP administration	same as section: <b>Common elements among 4 pivotal studies</b>	
Prohibited concomitant therapy (same as main study)	-any diabetic treatment other than study treatment, bolus insulin and metformin -systemic glucocorticoids>10 days -weight loss drugs	
Rescue medication	not applicable	unchanged from Main study- see Rescue medication section under EFC11629 (above)
Assessment for compliance	-patients documented daily the time of basal insulin injection in diary for the 7 days before visit/phone call -patients returned IMP to study site	
IMP Treatment allocation after completion of 3 month substudy to end of study	<b>HOE901-U300 adaptable dosing could:</b> <ul style="list-style-type: none"> <li>- continue using adaptable dosing</li> <li>or</li> <li>- revert to the fixed dosing intervals regimen</li> </ul> <b>HOE901-U300 fixed dosing:</b> <ul style="list-style-type: none"> <li>- continued fixed dosing regimen</li> </ul>	
Statistics		
Sample size	<b>-No sample size was determined.</b>	
Power	The power (for achieving an upper confidence limit of the 2-sided 95% CI not exceeding 0.4%) of the analysis of the primary endpoint was calculated based on different sample sizes and standard deviations (SD). These calculations assume that the true difference between the 2 regimen groups of the 3-month administration substudy would be zero in change in HbA1c and that all patients would be evaluable. Assuming that 100 patients per regimen group would be evaluable and the observed SD was 1.0%, the power would be 80%.	
Safety analyses	-conducted according to the regimen allocated as per the second randomization.	

Efficacy analysis	-all efficacy variables were evaluated from Month 6 up to Month 9 -early termination: the last postbaseline on-treatment efficacy measurement during the 3-month administration substudy period was used as the efficacy value at Month 9 (using last observation carried forward [LOCF] procedure).  -Primary and secondary efficacy variables were analyzed using an analysis of covariance (ANCOVA).  <b>No testing procedure was applied for primary and secondary efficacy endpoints; therefore, no multiplicity adjustment was made.</b>  The 3-month substudy treatment period for efficacy variables was defined as the time from Month 6 up to Month 9	
	-rescue not applicable	-For rescue patients, the last postbaseline efficacy measurement before the rescue and during 3-month substudy treatment period was used as the efficacy endpoint.

**Substudy EFC11628 and substudy EFC11629:**

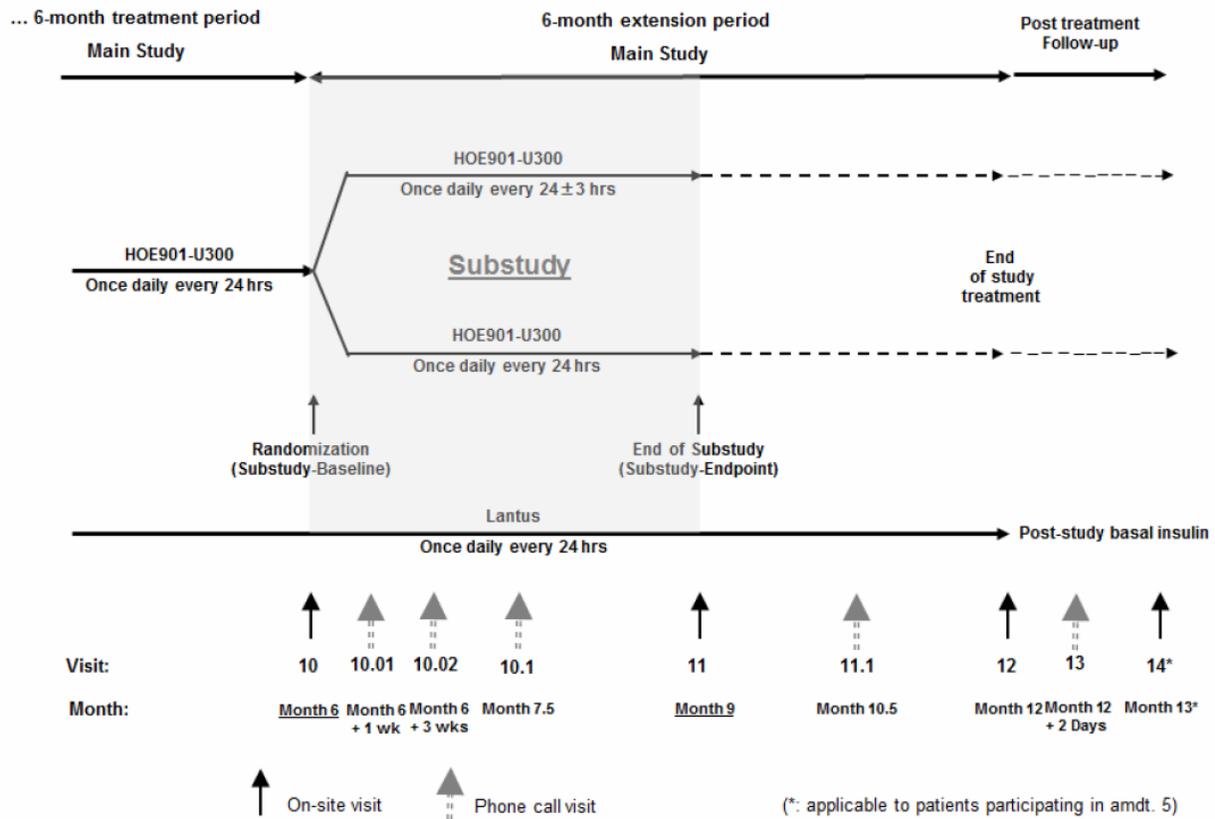
Figure 36 shows the timeline of Main study treatment period, Main study extension period (with embedded substudy), and follow up period. Figure 37 shows the visits for substudy EFC11628 and substudy EFC11629.

Figure 36 - Study design Substudy EFC11628 and EFC11629



Source: Study CSR

**Figure 37 - EFC 11628 substudy and EFC11629 patient visits**



Overall, both substudies had the same study timeline and patient visits.

**Substudy EFC11628:**

**Disposition of patients- substudy EFC11628**

Of the patients' (N=374) randomized to HOE901-U300 in the pivotal study EFC11628, less than a third (N=109) were randomized to the 2 dosing interval regimens:

- HOE901-U300 adaptable dosing : N=53
- HOE901-U300 fixed dosing : N=56

There were 4 reasons for non-inclusion in the substudy:

- IVRS/IWRS not gone live
- Substudy amendment still pending approval at site
- Patients declined participation
- Other reasons (such as Investigator decision for individual patients, technical/operational issues).

**Populations analyzed in substudy EFC11628:**

Safety population: 109 randomized patients exposed to the study treatment

Modified Intention-to-Treat (mITT): 108 subjects

-1 patient in the HOE901-U300 adaptable dosing interval (1/56, 1.8%) discontinued the substudy prematurely due to personal reasons after the baseline of the substudy. The discontinuation was not due to any hypoglycemic event or any physical complaints/symptoms. See

Table 71 for details on patient disposition.

**Table 71 - Substudy EFC11628 - Patient disposition**

	HOE901-U300 Adaptable Dosing Intervals	HOE901-U300 Fixed Dosing Intervals	All
Randomized sub-study population	56 (100%)	53 (100%)	109 (100%)
Efficacy sub-study populations			
Modified Intent-to-Treat (mITT)	55 (98.2%)	53 (100%)	108 (99.1%)
Sub-study completers	55 (98.2%)	53 (100%)	108 (99.1%)
Safety sub-study population	56	53	109

Note: patients are tabulated according to their randomized treatment.  
Source: study CSR

See Table 72 for details pertaining to protocol deviations potentially affecting efficacy analyses. Of the 108 patients in the mITT, 106 were evaluable.

**Table 72 - Substudy EFC11628 - Important protocol deviations potentially affecting efficacy analyses- Randomized substudy population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=53)
Any important deviations potentially impacting efficacy analyses	1 (1.8%)	2 (3.8%)
Important deviation resulting in exclusion of the patient from mITT sub-study population		
Patient randomized but not treated	0	0
No baseline (month 6) and/or post baseline efficacy endpoint during the 3-month comparative regimen period	1 (1.8%)	0
Important deviation not resulting in exclusion from mITT sub-study population		
No baseline (month 6) HbA1c value	0	0
No post-baseline HbA1c value during the 3-month comparative regimen period	0	2 (3.8%)

Note: Percentages are calculated using the number of patients randomized as denominator.  
Source: Study CSR

### ***Demography Substudy EFC11628***

The demographic and baseline characteristics were similar between the fixed dosing and adaptable dosing groups. Baseline characteristics included: >50% of patients being female, with a predominance of Caucasian/White participants (>90%). Use of concomitant diabetes and non-diabetes medications was similar among participants in the HOE901-U300 every 24 hours or HOE901-U300  $24 \pm 3$  hours. ~40-50% of participants in each dosing group took some formulation of biguanides during the substudy period. >96% of patients in either regimen took at least 1 non-antidiabetic medication during the substudy period (data available in Sponsor's substudy CSR).

Use of non-permitted concomitant medication was seen equally in both treatment groups, 4 patients (1 patient in the HOE901-U300 adaptable dosing intervals group and 3 patients in the HOE901-U300 fixed dosing intervals group) who reportedly took commercial insulin glargine. One of these patients (fixed dosing intervals group) took insulin glargine for 3 days. The 3 other cases involved insulin glargine that was discontinued prior to start of study IMP during the substudy, but the date of discontinuation was not reported. Furthermore, 1 patient (fixed dosing intervals group) took concomitant insulin isophane human during 4 periods of hospitalization for 57 days.

**Table 73 - Substudy EFC11628 - participant baseline characteristics-Randomized substudy population**

	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=53)	All (N=109)
<b>Age (years)</b>			
Number	56	53	109
Mean (SD)	61.0 (7.4)	59.1 (9.6)	60.1 (8.6)
Median	61.0	61.0	61.0
Min : Max	40 : 77	28 : 74	28 : 77
<b>Age Group (years) [n(%)]</b>			
Number	56	53	109
<65	36 (64.3%)	38 (71.7%)	74 (67.9%)
[65-75[	18 (32.1%)	15 (28.3%)	33 (30.3%)
≥75	2 (3.6%)	0	2 (1.8%)
<b>Gender [n (%)]</b>			
Number	56	53	109
Male	24 (42.9%)	25 (47.2%)	49 (45.0%)
Female	32 (57.1%)	28 (52.8%)	60 (55.0%)
<b>Race [n (%)]</b>			
Number	56	53	109
Caucasian/White	51 (91.1%)	51 (96.2%)	102 (93.6%)
Black	5 (8.9%)	1 (1.9%)	6 (5.5%)
Asian/Oriental	0	1 (1.9%)	1 (0.9%)
Other	0	0	0
<b>Ethnicity [n (%)]</b>			
Number	56	53	109
Hispanic	4 (7.1%)	4 (7.5%)	8 (7.3%)
Not Hispanic	52 (92.9%)	49 (92.5%)	101 (92.7%)
<b>World region [n (%)]</b>			
Number	56	53	109
North America	20 (35.7%)	14 (26.4%)	34 (31.2%)
Western Europe	3 (5.4%)	3 (5.7%)	6 (5.5%)
Eastern Europe	29 (51.8%)	30 (56.6%)	59 (54.1%)
Rest of the world	4 (7.1%)	6 (11.3%)	10 (9.2%)

Source: Substudy CSR

**Measurement of treatment and dosing interval regimen compliance Substudy EFC11628**

In substudy EFC11628, patients' were responsible for reporting injection time for the last 7 days before the on-site visits at Month 7.5 and Month 9 with a maximum of **12 injection intervals** and **14 injection times**. Data of HOE901-U300 administration was available in 106 of 107 patients.

**Reviewer's comments: The documentation of injection time of basal insulin by patients is a potential source of bias.** (b) (4)

At substudy baseline for both the injection interval between 2 consecutive injections and the average time between injection and reference injection was similar in both groups. The mean time interval between 2 consecutive injections for adaptable dosing vs. fixed dosing was: 24.05 hours versus 24.00 hours respectively. Similarly, the time interval between injection and reference time was 24.03 hours vs. 24.20 hours for adaptable dosing and fixed dosing regimens respectively.

To assess for compliance, the Sponsor assessed injection time between the following:

- 1) 2 consecutive injections
- 2) Actual injection time and the reference injection

**1) Compliance was assumed for 2 consecutive injections using algorithm below. A visual depiction of this algorithm is seen in Figure 38:**

- Adaptable dosing intervals
  - $\geq 4$  injections were done in the  $>26.5$  hours or  $<21.5$  hour time interval and/or
  - $\geq 5\%$  injections by patient were done at time intervals  $<23$  or  $>25$  hours
- Fixed dosing interval
  - $>80\%$  of 2 consecutive injections per patient were done in the 23 to 25 time interval

**Figure 38 - Definitions of compliance based on 2 consecutive injections of both adaptable dosing and fixed dosing- substudy EFC11628**

Hours between consecutive injections	Less than 21.5	21.5	23	25	26.5	Greater than 26.5
injection number	$\geq 4$	OR				$\geq 4$
Adaptable dosing						
injection percentage	$\geq 5\%$	and/or		$\geq 5\%$		
Fixed dosing						
injection percentage	$>80\%$					

The results of injection time between 2 consecutive injection administrations based on the algorithm depicted in Figure 38 are shown in Table 76.

**Table 74 - Patients by injection interval between 2 consecutive injections- Safety substudy population – EFC11628**

Number (%) of patients with	HOE901-U300 Adaptable Dosing Intervals (N=56)	HOE901-U300 Fixed Dosing Intervals (N=53)
≥12 injection intervals in the range of [23-25] hours	7/55 (12.7%)	29/51 (56.9%)
100% of injection intervals in the range of [23-25] hours	8/55 (14.5%)	34/51 (66.7%)
≥4 injection intervals >25 hours or <23 hours	29/55 (52.7%)	8/51 (15.7%)
≥4 injection intervals >25 hours	14/55 (25.5%)	4/51 (7.8%)
≥4 injection intervals <23 hours	12/55 (21.8%)	4/51 (7.8%)
≥4 injection intervals >26.5 hours or <21.5 hours	17/55 (30.9%)	3/51 (5.9%)
≥4 injection intervals >26.5 hours	9/55 (16.4%)	1/51 (2.0%)
≥4 injection intervals <21.5 hours	7/55 (12.7%)	0/51

Note: Number of injections (time between 2 consecutive injections) is calculated using all injection intervals  
Source: Substudy CSR

**Reviewer’s comment:**

**Table 74 shows that there is variability of dosing in both the adaptable and fixed dosing interval groups. The adaptable dosing group had greater percentage of ≥4 injections at intervals >25 or <23 hours as well as >26 or <21 hours. The Fixed dosing intervals group, however, did not meet the specified compliance of >80% of 2 consecutive injections per patient done in the 23-25 time interval. In fact, 29/51 or 56.9% of ≥12 injection intervals were in the range of 23-25 hours.**

- 2) Compliance between **injection time and reference injection time** was assumed if 80% of the injection times followed the following algorithm:
  - Adaptable dosing intervals: injection time= 3 hours earlier or later than reference injection time
  - Fixed dosing intervals: injection time=reference injection time

According to the Sponsor, compliance between injection time and reference injection time was met due to the the small number of deviations (> 3 hours) from the reference injection time in both the adaptable and fixed dosing intervals.

- adaptable dosing intervals group:
  - 0.9% between 6 and7 hours before
  - 0.4% between 4 and 5 hours before
  - 2.1% between 3 to 4 hours before
  - 3.6% between 3 to 4 hours after

- 1.2% between 4 and 5 hours after
- fixed dosing intervals group:
  - 0.9% between 2 and 3 hours before
  - 1.9% between 2 to 3 hours after
  - 0.3% between 3 after 4 hours after

**Reviewer’s comments: Although a small number of deviations over 3 hrs are seen in the adaptable and fixed dosing interval groups, hours>5 are not shown, therefore making this list incomplete. The Sponsor does not clearly show if indeed 80% of the injection times followed the prespecified algorithm in bullet “2)” above.**

***Efficacy Evaluation for EFC11628***

Pre-specified efficacy endpoints are listed in Table 70. The least square mean change in HbA1c from Month 6 to Month 9 was similar in both dosing regimens, see Table 75. There was a LS mean difference±SE of 0.21±0.11% between the adaptable dosing and fixed dosing intervals.

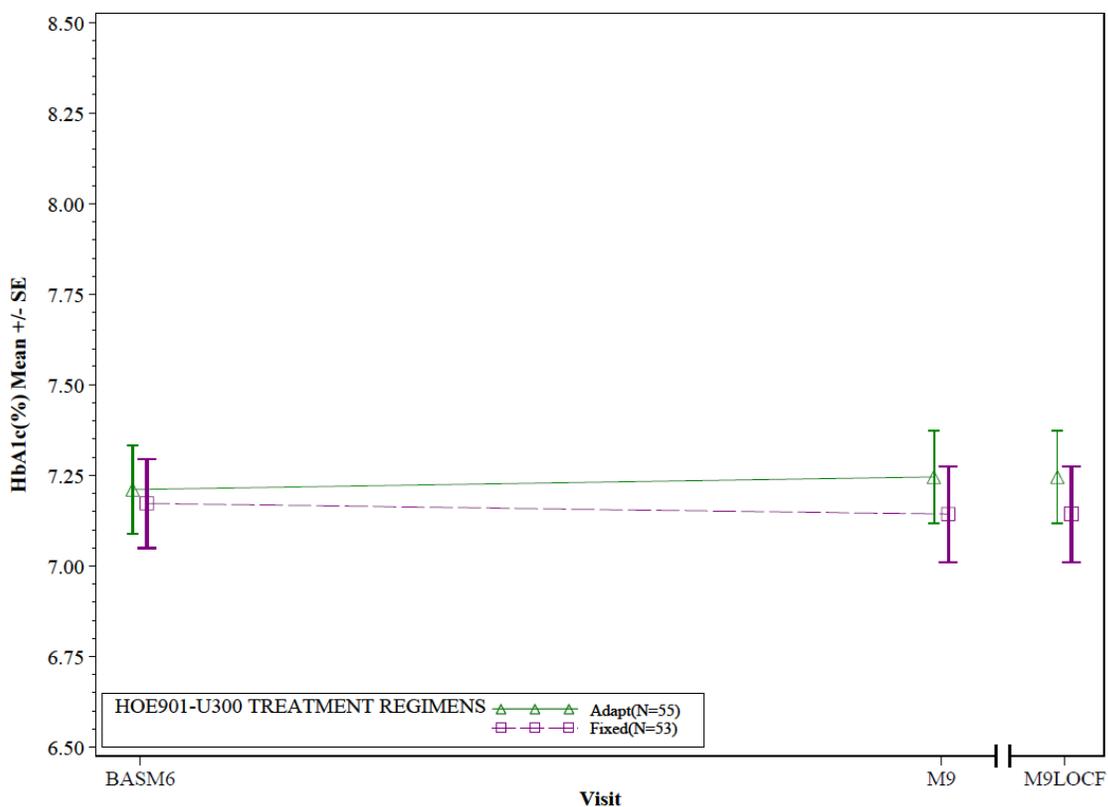
**Table 75 - Substudy EFC11628 - Main efficacy analysis- Mean change in HbA1c (%) from baseline (Month 6)**

HbA1c (%)	HOE901-U300 Adaptable Dosing Intervals (N=55)	HOE901-U300 Fixed Dosing Intervals (N=53)
<b>Baseline (Month 6)</b>		
Number	55	51
Mean (SD)	7.21 (0.91)	7.17 (0.89)
<b>Month 9 endpoint (LOCF)</b>		
Number	55	51
Mean (SD)	7.25 (0.96)	7.14 (0.96)
<b>Δ from baseline to Month 9 (LOCF)</b>		
Number	55	51
Mean (SD)	0.03 (0.56)	-0.03 (0.72)
LS Mean (SE) <sup>a</sup>	0.21 (0.111)	0.15 (0.120)
LS Mean difference (SE) vs. HOE901-U300 fixed dosing intervals <sup>a</sup>	0.05 (0.123)	
95%CI	(-0.189 to 0.298)	

LOCF = Last observation carried forward.

<sup>a</sup> Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline HbA1c value as a covariate.

**Figure 39 – Substudy EFC11628 - Main efficacy analysis- Mean HbA1c (%) by visit during the 3-month comparative regimen period- mITT substudy population**



# subjects		Visit	
Adapt(N=55)	55	M9	55
Fixed(N=53)	51	M9LOCF	51

BASM6 = Baseline (month 6), M9LOCF= last value during the 3-month comparative regimen period (LOCF).  
Source: Substudy CSR

**Secondary efficacy results - substudy EFC11628**

The mean change in fasting plasma glucose from Month 6 to Month 9 was small and similar between the adaptable and fixed dosing groups with a LS mean±SE difference of 4.85mg/dL (95%CI: -10.622 to 20.314). Similarly, minor changes in the average daily basal insulin and total daily insulin doses were observed in the substudy period for both dosing regimen (information not show in this review).

**Substudy EFC11629**

**Disposition of patients- substudy EFC11629**

Of the patients' (N=344) randomized to HOE901-U300 in the pivotal study EFC11629, less than a third (N=89) were randomized to the 2 dosing interval regimens:

- HOE901-U300 adaptable dosing : N=45
- HOE901-U300 fixed dosing : N=44

The same 4 reasons for non-inclusion in substudy EFC11628 as in substudy EFC 11628 (see above)

*Populations analyzed in substudy EFC11629 (see Table 76):*

Safety population: 87 patients were exposed to the study treatment

Modified Intention-to-Treat (mITT): 86

-1 patient in the HOE901-U300 adaptable dosing interval (1/45, 2.2%) discontinued the substudy prematurely due to personal reasons, “not safety.”

-2 patients in the in the HOE901-U300 fixed dosing interval (2/44, 4.5%) discontinued the substudy due to poor compliance (1 patient) and lack of interest, but “not safety related” (1 patient).

All rescue medication administered during the 3-month substudy was started during the main 6-month study and was continued. Patients that received rescue therapy were included in mITT, but were considered non-evaluable for efficacy analysis. These patients were:

- 3 patients (6.7%) randomized to the HOE901-U300 adaptable dosing interval regimen.
- 2 patients (4.5%) randomized to the HOE901-U300 fixed dosing interval regimen.

No patient discontinued the substudy while continuing the IMP in the main study.

**Table 76 - Substudy EFC11629 - analysis population**

	HOE901-U300 Adaptable Dosing Intervals	HOE901-U300 Fixed Dosing Intervals	All
Randomized sub-study population	45 (100%)	44 (100%)	89 (100%)
Efficacy sub-study populations			
Modified Intent-to-Treat (mITT)	44 (97.8%)	42 (95.5%)	86 (96.6%)
Sub-study completers	40 (88.9%)	38 (86.4%)	78 (87.6%)
Safety sub-study population	44	43	87

Source: substudy CSR

See Table 77 for details regarding protocol violations. Of the 86 patients randomized, 3 patients were not evaluable.

**Table 77 - Substudy EFC11629 - protocol deviations potentially impacting efficacy analyses-Randomized substudy population**

	<b>HOE901-U300 Adaptable Dosing Intervals (N=45)</b>	<b>HOE901-U300 Fixed Dosing Intervals (N=44)</b>
Any important deviations potentially impacting efficacy analyses	5 (11.1%)	7 (15.9%)
Important deviation resulting in exclusion of the patient from mITT sub-study population	1 (2.2%)	2 (4.5%)
Patient randomized but not treated	1 (2.2%)	1 (2.3%)
No baseline (month 6) and/or post baseline efficacy endpoint during the 3-month comparative regimen period	1 (2.2%)	2 (4.5%)
Important deviation not resulting in exclusion from mITT sub-study population	4 (8.9%)	5 (11.4%)
No baseline (month 6) HbA1c value	0	1 (2.3%)
No post-baseline HbA1c value during the 3-month comparative regimen period and before rescue if any	4 (8.9%)	4 (9.1%)

Note: Percentages are calculated using the number of patients randomized as denominator.

### ***Demography Substudy EFC11629***

The demographic and baseline characteristics were similar between the fixed dosing and adaptable dosing groups. Baseline characteristics included: >50% of patients being female, with a predominance of Caucasian/White participants (>90%). See Table 79 for demography details.

Use of concomitant diabetes and non-diabetes medications was similar among participants in the fixed or adaptive dosing intervals. More than 95% of participants in both groups took biguanides. Ninety-five percent of patients in both groups received at least 1 non-antidiabetic medication during the substudy period. Details of these medications are available in the substudy CSR.

**Table 78 - Substudy EFC11629 - Antidiabetic medications taken by patients- Safety substudy population**

Chemical Class Standardized medication name	Intervals (N=44)	Dosing Intervals (N=43)
Any anti-diabetic concomitant medications	44 (100%)	42 (97.7%)
Blood glucose lowering drugs, excl. insulins	44 (100%)	42 (97.7%)
Biguanides	44 (100%)	41 (95.3%)
Metformin	35 (79.5%)	35 (81.4%)
Metformin hydrochloride	9 (20.5%)	6 (14.0%)
Dipeptidyl peptidase 4 (dpp-4) inhibitors	3 (6.8%)	3 (7.0%)
Sitagliptin phosphate	3 (6.8%)	2 (4.7%)
Linagliptin	0	1 (2.3%)
Sitagliptin	0	1 (2.3%)
Sulfonamides, urea derivatives	2 (4.5%)	0
☆ Glimepiride	2 (4.5%)	0
Combinations of oral blood glucose lowering drugs	1 (2.3%)	0
Eucreas	1 (2.3%)	0
Other blood glucose lowering drugs, excl. insulins	1 (2.3%)	1 (2.3%)
☆ Liraglutide	1 (2.3%)	0
Repaglinide	0	1 (2.3%)
Alpha glucosidase inhibitors	0	1 (2.3%)
Acarbose	0	1 (2.3%)
Thiazolidinediones	0	1 (2.3%)
Pioglitazone hydrochloride	0	1 (2.3%)
Insulins and analogues	1 (2.3%)	2 (4.7%)
Insulins and analogues for injection, fast-acting	1 (2.3%)	2 (4.7%)
☆ Insulin glulisine	1 (2.3%)	0
☆ Insulin aspart	0	2 (4.7%)

☆ Patients who received rescue therapy (all were started during the main 6-month study and continued during the substudy).

Table 78 shows similar distribution of anti-diabetic medications taken for the 3-month duration of the substudy, in the adaptable and fixed dosing groups. All rescue medicines were started during the main 6-month study period and continued during the substudy. In total 5/87 (5.7%) patients required rescue therapy. These patients were distributed evenly between the adaptable, 3/44 (6.8%) and fixed, 2/43 (4.7%) groups.

**Table 79 – Substudy EFC11629 - Demographics and patient characteristics at baseline-  
Randomized substudy population**

	<b>HOE901-U300 Adaptable Dosing Intervals (N=45)</b>	<b>HOE901-U300 Fixed Dosing Intervals (N=44)</b>	<b>All (N=89)</b>
<b>Age (years)</b>			
Number	45	44	89
Mean (SD)	58.4 (8.2)	57.2 (10.0)	57.8 (9.1)
Median	59.0	57.0	58.0
Min : Max	27 : 72	33 : 84	27 : 84
<b>Age Group (years) [n(%)]</b>			
Number	45	44	89
<65	36 (80.0%)	37 (84.1%)	73 (82.0%)
[65-75[	9 (20.0%)	6 (13.6%)	15 (16.9%)
≥75	0	1 (2.3%)	1 (1.1%)
<b>Gender [n (%)]</b>			
Number	45	44	89
Male	22 (48.9%)	22 (50.0%)	44 (49.4%)
Female	23 (51.1%)	22 (50.0%)	45 (50.6%)
<b>Race [n (%)]</b>			
Number	45	44	89
Caucasian/White	42 (93.3%)	40 (90.9%)	82 (92.1%)
Black	3 (6.7%)	3 (6.8%)	6 (6.7%)
Asian/Oriental	0	0	0
Other	0	1 (2.3%)	1 (1.1%)
<b>Ethnicity [n (%)]</b>			
Number	45	44	89
Hispanic	5 (11.1%)	7 (15.9%)	12 (13.5%)
Not Hispanic	40 (88.9%)	37 (84.1%)	77 (86.5%)
<b>World region [n (%)]</b>			
Number	45	44	89
North America	22 (48.9%)	29 (65.9%)	51 (57.3%)
Western Europe	3 (6.7%)	1 (2.3%)	4 (4.5%)
Eastern Europe	20 (44.4%)	13 (29.5%)	33 (37.1%)
Rest of the world	0	1 (2.3%)	1 (1.1%)

Source: Study CSR

Patients' were responsible for reporting injection time for the last 7 days before the on-site visits at Month 7.5 and Month 9 with a maximum of **12 injection intervals** and **14 injection times**. Data of HOE901-U300 administration in was available in 86 of 87 patients.

**Reviewer's comments: The documentation of injection time of basal insulin by patients is a potential source of bias.** (b) (4)

At substudy baseline, the injection interval between 2 consecutive injections was similar in both groups. The average time between injection and reference injection time was also similar in both groups. The mean time interval between 2 consecutive injections for adaptable dosing vs. fixed dosing was 23.98 hours versus 23.99 hours respectively. Similarly, the time interval between injection and reference time was 24.13 hours vs. 24.20 hours for the adaptable dosing and fixed dosing regimens respectively.

The Sponsor's dual **assessment** of compliance (by 1. consecutive injections and 2. time between injection and reference time) was the same as in substudy EFC11628. The Sponsor's **assumption** of compliance by these two methods is also the same as substudy EFC 11628. See Figure 38 above.

Table 80 shows assessment by consecutive injections. Overall, the adaptable dosing group had a greater number of injections at >26 and <21.5 hours than the fixed dosing group. The mean percentage of injections by patient administered within a 23 to 25 hour interval in the fixed dosing interval group was 88.77% (data not shown).

**Table 80 - Patients by injection interval between 2 consecutive injections- Safety substudy population – EFC11629**

Number (%) of patients with	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=43)
≥12 injection intervals in the range of [23-25] hours	4/40 (10.0%)	17/39 (43.6%)
100% of injection intervals in the range of [23-25] hours	6/40 (15.0%)	24/39 (61.5%)
≥4 injection intervals >25 hours or <23 hours	27/40 (67.5%)	5/39 (12.8%)
≥4 injection intervals >25 hours	18/40 (45.0%)	1/39 (2.6%)
≥4 injection intervals <23 hours	13/40 (32.5%)	1/39 (2.6%)
≥4 injection intervals >26.5 hours or <21.5 hours	19/40 (47.5%)	1/39 (2.6%)
≥4 injection intervals >26.5 hours	7/40 (17.5%)	0/39
≥4 injection intervals <21.5 hours	3/40 (7.5%)	1/39 (2.6%)

Note: Number of injections (time between 2 consecutive injections) is calculated using all injection intervals

Source: Study CSR

**Reviewer's comment:** [REDACTED] (b) (4)

According to the Sponsor, compliance between injection time and reference injection time was met due to the small number of deviations (>3 hours) from the reference injection time in both the adaptable and fixed dosing intervals.

- adaptable dosing intervals group:
  - 1.3% between 3 to 4 hours before
  - 5.2% between 3 to 4 hours after
  - 0.6% between 4 and 5 hours after
- fixed dosing intervals group:
  - 2.7% between 3 and 4 hours after
  - 1.7% between 3 after 4 hours before
  - 0.8% between 4 and 5 hours before
  - 0.4% between 4 and 5 hours after
  - 0.4% between 5 and 6 hours after

**Reviewer's comments:** A small number of deviations over 3 hrs are seen in both adaptable and fixed dosing interval groups; however this data is based on patient's documentation of when they injected their insulin dose. Documentation by patients could be a source of recall bias and thus not accurately depict the time of injection.

***Efficacy Evaluation for EFC11629***

Pre-specified efficacy endpoints are listed in Table 70. The least square mean change in HbA1c from Month 6 to Month 9 was similar in both dosing regimens, see Table 81. There was an adjusted LS mean difference±SE of 0.13±0.142% between the adaptable dosing and fixed dosing intervals with 95% CI of -0.152 to 0.415).

**Table 81 - Substudy EFC11629 - Main efficacy analysis - Mean change in HbA1c (%) from baseline (Month 6)**

HbA1c (%)	HOE901-U300 Adaptable Dosing Intervals (N=44)	HOE901-U300 Fixed Dosing Intervals (N=42)
<b>Baseline (Month 6)</b>		
Number	40	37
Mean (SD)	7.41(0.96)	7.47 (1.05)
<b>Month 9 endpoint (LOCF)</b>		
Number	40	37
Mean (SD)	7.47 (0.87)	7.49 (1.11)
<b>Δ from baseline to Month 9 (LOCF)</b>		
Number	40	37
Mean (SD)	0.06 (0.64)	0.02 (0.63)
LS Mean (SE) <sup>a</sup>	-0.12 (0.151)	-0.25 (0.162)
LS Mean difference (SE) vs. HOE901-	0.13 (0.142)	

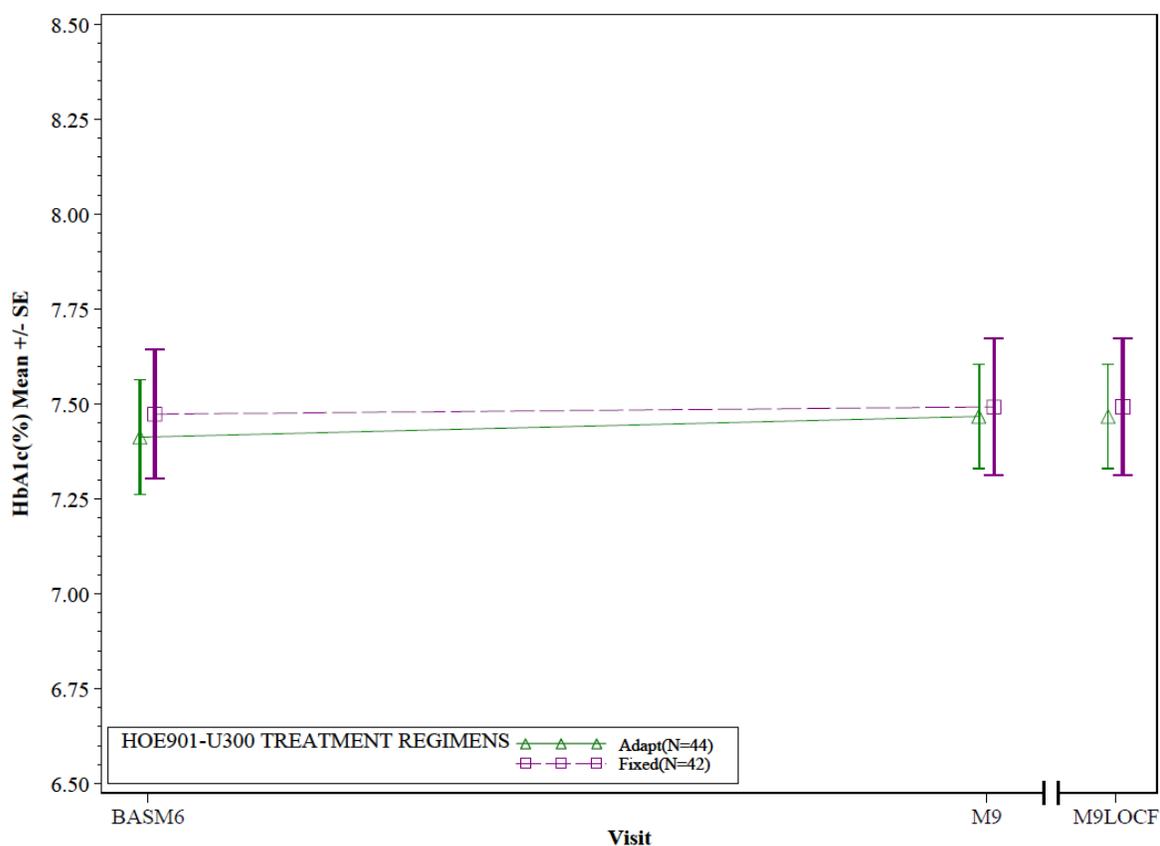
U300 fixed dosing intervals <sup>a</sup>		
95%CI	(-0.152 to 0.415)	

LOCF = Last observation carried forward.

<sup>a</sup> Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline HbA1c value as a covariate.

**Reviewer’s comment:** Table 81 shows that there was a small LS mean difference in the mean change in HbA1c between the adaptable and fixed dosing interval groups. This difference is shown in Figure 40.

**Figure 40 –Substudy EFC11629 - Main efficacy analysis- Mean HbA1c (%) by visit during the 3- month comparative regimen period - mITT substudy population**



# subjects

Adapt(N=44) 40

Fixed(N=42) 37

40 40

37 37

Source: Study CSR

Secondary efficacy results - substudy EFC11629 between the adaptable and fixed dosing groups with a LS mean±SE difference of -3.74mg/dL (95%CI: -21.609 to 14.132). Similarly, minor changes in the average daily basal insulin and total daily insulin doses were observed in the substudy period for both dosing regimen (information not show in this review).

**Reviewer’s comment:**

(b) (4)

**Because compliance in substudy EFC11628 and substudy 11629, relied on the patients' documentation, interpretation of the results of HbA1c and FPG may be affected by bias. The fixed dosing interval group had variability in their insulin administration times. Likewise the adaptable dosing group had intervals of consistent non-variable dosing (which was allowable since injections had to vary by  $24 \pm 3$  hours for a minimum of 2 days a week). The homogeneity in the dosing of the two groups (i.e. the presence of nonvariable time in the adaptable doing group and variable time in the fixed dosing group) makes it difficult to interpret the difference between them**

(b) (4)

#### Assessment of safety of adaptable vs. fixed dosing intervals

During the EFC11628 substudy period, 4 of 56 patients (7.1%) on the HOE901-U300 adaptable dosing intervals regimen and 5 of 53 patients (9.4%) on the HOE901-U300 fixed dosing intervals regimen had at least 1 serious adverse event. In the EFC11629 substudy period, 2 of 44 patients (4.5 %) on HOE901-U300 adaptable dosing interval regimen had at least 1 serious adverse event. There were no SAEs reported by patients on HOE901-U300 fixed dosing interval.

None of the events in the substudy groups was related to serious events of hypoglycemia.

**Reviewer's comment: There were no imbalances noted in the rates of serious adverse events between the adaptable and fixed dosing HOE901-U300 groups.**

Within all substudies (substudy EFC11628 and substudy EFC 11629), severe hypoglycemia was documented only in 1 patient (in substudy EFC11628 fixed dosing interval).

#### **7.4.6 Immunogenicity**

In this section, the reviewer evaluates differences in AIA data (both antibody status and antibody titer) in patients randomized to HOE901-U300 vs. Lantus. In pre-submission regulatory correspondence, the Sponsor communicated that they revalidated the RIP (isotopic) assay submitted in the original Lantus NDA. This revalidated RIP assay was implemented in the Phase 3 clinical trials. In the Pre-NDA minutes, the Agency agreed with the Sponsor's proposal that AIA (anti-insulin antibodies) assessment of patients with T2DM (of trials: EFC11628 and EFC11629) who have completed the 6-month main study period, would be presented in the NDA. "The AIA results after completion of the 12-month study duration for these patients and

AIA results after completion of the 6-month main study periods and 12-month study duration for insulin naïve patients with T2DM (EFC12347) and patients with T1DM (EFC12456) will be provided post approval.” It was also documented that it is not feasible to assess reversibility of anti-insulin antibodies, during a washout period, since these patients need daily insulin to control their diabetes.

The Sponsor’s definition of AIA status and titer categories are as follows:

- Anti-insulin antibody status (positive, negative): A patient is defined as AIA positive if the patient is positive at any time during the main 6-month on-treatment period.
- Anti-insulin antibody titer category (low, high): AIA titer categories are defined for an AIA positive patient using the maximal titer value over the main 6-month on-treatment period. Categories are based on actual data and are defined as low if the maximal titer is <64 and as high if the maximal titer is ≥64.

In all trials, samples were analyzed at a centralized laboratory using a validated AIA binding assay methodology for AIA status, titer, and cross-reactivity to human insulin. In all discussed trials, patients had prior exposure to insulin.

The analysis of the AIA data is interpreted by evaluating the incidence of severe hypoglycemia, differences in glycemic control e.g. HbA1c, and differences in other TEAEs between treatment groups

#### T1DM (EFC12456)

At baseline, a similar percentage of HOE901-U300 (169/274, 61.7%) and Lantus patients (147/275, 53.6%) were positive for AIA. Throughout the main 6-month on-treatment period, the percentage of AIA-positive patients slightly increased with increasing exposure. ~78% of patients in either treatment group had a positive AIA status during the 6 month on treatment period. Among these patients, the percentage of those with antibodies cross-reacting with human insulin was similar between treatment groups, and ranged from 78% to 87%. Equal number of patients (26 patients) in either treatment group had high AIA titers.

Half as many patients in the HOE901-U300 AIA positive patients experienced severe hypoglycemia compared to Lantus (11, [5.3%] vs. 22 [10.4%]). See Table 82. When analyzed by titers, there were more patients with high AIA titers in the HOE901-U300 group (3 patients) vs. the Lantus group (1 patient), who experienced severe hypoglycemia (see **Table 83** and **Table 83**).

**Table 82 - EFC 12456 - Safety population with at least one AIA status during the main 6-month on treatment period who experienced severe hypoglycemia.**

	Anti-insulin antibody status			
	Negative		Positive	
	HOE901-U300 N=57	Lantus N=58	HOE901-U300 N=209	Lantus N=212
Severe hypoglycemia	7 (12.3%)	4 (6.9%)	11 (5.3%)	22 (10.4%)

A patient is defined as AIA positive if the patient is positive at any time during the main 6-month on-treatment period  
Source modified CSR EFC12456-Table section 16.2.7.4.6.1.1

**Table 83 - EFC 12456-Safety population with at least one AIA status during the main 6-month on treatment period who experienced severe hypoglycemia by AIA titer**

	Anti-insulin antibody titer			
	Low		High	
	HOE901-U300 N=182	Lantus N=185	HOE901-U300 N=26	Lantus N=26
Severe hypoglycemia	8 (4.4%)	21 (11.4%)	3 (11.5%)	1 (3.8%)

AIA titer categories are defined on patient positive at any time during the main 6-month on-treatment period using maximal titer. Categories are based on actual data and defined as low if  $2 \leq \text{maximal titer} < 64$  and as high if maximal titer  $\geq 64$   
Source modified CSR EFC12456-Table section 16.2.7.4.6.2.1

**Reviewer’s comment: Although more patients (with high titers) experienced severe hypoglycemia in the HOE901-U300 than the Lantus group, it is important to note the small size of this subset. Overall, the small sizes in these subgroups limit interpretation of the data.**

The number of patients experiencing at least one injection site reaction TEAE and having a positive AIA was similar between HOE901-U300 and Lantus (4/209 [1.9%] vs. 3/212 [1.4%] respectively). There were no injection site reactions reported in the high titer group in neither the HOE901-U300 or Lantus group.

Twelve of the 16 patients in the HOE901-U300 group and 12 of the 13 patients in the Lantus group who experienced hypersensitivity reactions during the main 6-month on-treatment period were positive for AIA; none of these patients was in the high titer group.

There was no apparent difference in HbA1c change from baseline to Month 6, between patients with positive antibody status randomized to HOE901-U300 or Lantus. However, when evaluating patients with high antibody titers, a difference favoring Lantus was seen (see Table 86). Patients with high titers in the HOE901-U300 group had a smaller change of HbA1c from baseline to month 6, compared to patients with high titers, randomized to Lantus.

**Reviewer’s comment: Given the small number of patients with high AIA titers, the differences in HbA1c must be interpreted cautiously.**

T2DM (EFC11628 and EFC11629)

The pooled AIA data for studies EFC11628 and EFC11629 in patients with T2DM is discussed in this section. Neither of these studies included insulin naïve patients.

At baseline, a similar percentage of HOE901-U300 patients (327/807, 41.6%) and Lantus patients (296/808, 37.7%) were positive for AIA. During the main treatment period, the overall percentage of antibody positive patients remained similar between treatment groups. Including baseline, the percentage of AIA positive patients ranged from 37 to 44%, independent of the treatment group during all testing intervals. The percentage of patients showing a conversion of the antibody status from negative at baseline to positive slightly increased from 10% at Week 4 to about 20% in both groups at Month 6. The percentage of patients who converted from baseline positive to negative AIA was constant at about 20%.

Similar number of patients with positive AIA titers in the HOE901-U300 vs. Lantus groups (16 vs. 17 respectively) experienced at least one severe hypoglycemia event (see Table 84). When analyzed by AIA titers (Table 85), there were equal number of patients (2 patients) in each treatment group, with high AIA titers and who experienced at least one severe hypoglycemia event.

**Table 84 – Number (%) of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by anti-insulin antibody status during the main treatment period: T2DM studies**

Severe hypoglycemia per investigator	HOE901-U300	Lantus
	n/N(%)	n/N(%)
<u>T2DM - EFC11628</u>		
Number of patients	404	402
Overall	20/404 (5.0%)	23/402 (5.7%)
Negative	6/125 (4.8%)	6/120 (5.0%)
Positive <sup>a</sup>	14/277 (5.1%)	17/277 (6.1%)
<u>T2DM - EFC11629</u>		
Number of patients	403	406
Overall	4/403 (1.0%)	6/406 (1.5%)
Negative	2/255 (0.8%)	6/263 (2.3%)
Positive <sup>a</sup>	2/141 (1.4%)	0/135

<sup>a</sup> A patient status is defined as AIA positive if the patient is positive at any time during the main treatment period.  
Source: modified table ISS, section 6.2.6.5.1

**Reviewer’s comments: The number of patients who experienced severe hypoglycemia and had either positive AIA or high AIA titers was small. No definitive safety conclusions can be drawn this information.**

**Table 85 – Number (%) of patients with at least one hypoglycemia event (severe hypoglycemia as per investigator) by anti-insulin antibody titer categories during the main treatment period: T2DM studies**

Severe hypoglycemia per investigator	HOE901-U300	Lantus
	n/N(%)	n/N(%)
<b>T2DM - EFC11628</b>		
Number of patients	404	402
Overall	20/404 (5.0%)	23/402 (5.7%)
Low <sup>b</sup>	12/240 (5.0%)	15/245 (6.1%)
High <sup>b</sup>	2/35 (5.7%)	2/32 (6.3%)
<b>T2DM - EFC11629</b>		
Number of patients	403	406
Overall	4/403 (1.0%)	6/406 (1.5%)
Low <sup>b</sup>	2/116 (1.7%)	0/118
High <sup>c</sup>	0/24	0/16

<sup>b</sup> Titer categories are based on the maximum titer measured during the main treatment period. Categories are determined on actual data and defined as low if  $2 \leq \text{maximal titer} < 64$  and as high if  $\text{maximal titer} \geq 64$  (1/dil)  
Source: modified from ISS section 6.2.6.7.1

In both EFC11628 and EFC11629, there was no apparent difference in HbA1c change from baseline to Month 6, between patients with positive antibody status randomized to HOE901-U300 or Lantus. There was, however, a difference in change in HbA1c noted when evaluating patients with high AIA titers. In EFC11628, patients with high AIA titers in the HOE901-U300 group had a greater reduction in HbA1c at 6 months compared to baseline, whereas opposite results were seen in trial EFC11629 (See Table 86).

**Reviewer’s comments: The effects of high AIA titers on HbA1c, in combination with the small number of patients with high AIA titers, limits interpretation of the data.**

A difference between AIA-positive and -negative patients was seen in 2 TEAEs for both treatment groups together: arthralgia was reported in 25 AIA-positive patients (only 1 patient was in the high titer group) compared with 8 AIA-negative patients; peripheral edema was reported in 30 AIA-positive patients (5 patients in the high titer group) compared with 16 AIA-negative patients. Twenty of the 32 patients in the HOE901-U300 group and 16 of the 30 patients in the Lantus group who experienced hypersensitivity reactions during the main 6-month on-treatment period were positive for AIA; only 1 HOE901-U300-treated patient and 3 Lantus-treated patients were in the high titer group.

Overall, no specific safety signal for HOE901-U300 was detected based on the AIA status of the patients for common TEAEs, local tolerability at injection sites, or hypersensitivity reactions.

**Table 86 – Change in HbA1c from baseline to endpoint (Month 6) in patients with high titers**

Study (stats analysis)	Treatment group	baseline N	Baseline Mean	Endpoint Mean (SD)	Change from baseline		
					LS Mean (SE)	LSMean difference (SE) vs Lantus	LSMean difference (SE) vs Lantus
<b>Type 1 Diabetes</b>							
EFC12456 <sup>a</sup> (MMRM)	HOE901-U300	25	8.26	7.94 (0.68)	-0.17 (0.149)	<b>0.5 (0.207)</b>	<b>0.098 to 0.911</b>
	Lantus	26	7.86	7.28 (0.5)	-0.68 (0.143)		
<b>Type 2 Diabetes</b>							
EFC11628 (LOCF) <sup>b</sup>	HOE901-U300	18	8.18	7.16 (0.82)	-1.03 (0.189)	<b>-0.45 (0.265)</b>	<b>-0.972 to 0.072</b>
	Lantus	18	8.40	7.69 (1.73)	-0.58 (0.187)		
EFC11629 (LOCF) <sup>b</sup>	HOE901-U300	16	8.68	7.79 (0.94)	-0.75 (0.249)	<b>0.30 (0.421)</b>	<b>-0.529 to 1.131</b>
	Lantus	9	8.07	7.24 (0.75)	-1.05 (0.334)		
<sup>a</sup> MMRM analysis with randomized groups (HOE901-U300 Morning injection, HOE901-U300 Evening injection, Lantus Morning injection, Lantus Evening injection), randomization strata of screening HbA1c (<8.0,=8.0%), subgroup factor, visit (week 12, Month 6), visit-by-randomized group interaction, subgroup factor-by-randomized group, subgroup factor-by-visit-interaction and subgroup factor-by-randomized group-by-visit interaction as fixed categorical effects as well as baseline HbA1c value and baseline HbA1c-by-visit interaction as continuous fixed covariates. MMRM value is either the observed value at selected visit or value retrieved according to time windows defined in the SAP. <sup>b</sup> Analyse of covariance (ANCOVA) model with treatment group (HOE901-U300 and Lantus), randomization strata of screening HbA1c (<8.0, ≥8.0%), country, antibody subgroup and treatment-by-antibody subgroup interaction as fixed effect and baseline HbA1c as covariate. Month 6 endpoint is the last post baseline on treatment HbA1c measurement (LOCF) before initiation of rescue medication and -if no AIA data are available from the same visit-AIA determination obtained within ± 90 days of the HbA1c measurement applied							
Source: study EFC12456 CSR, Table 46; EFC11628, Table 38; EFC11629, Table 38							

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events for switching from HOE901-U300 to other insulins

The safety in converting from HOE901-U300 to other insulin products (including Lantus) was evaluated in the 4-week follow up period, reported in the 120 Day Safety Update from the completed studies (EFC11628 and EFC11629). Limited Phase 2 study information is also available for study PDY12777, submitted with the NDA. As mentioned throughout this review, the pharmacodynamic effect differences between HOE901-U300 and Lantus are concerning, especially when patients convert from an insulin with a lesser pharmacodynamic effect (i.e. HOE901-U300) to one with a higher pharmacodynamic effect (i.e. Lantus).

At the end of the 12-month treatment period (for Phase 3 studies) and 16-weeks (for PDY12777), patients were transitioned to a commercial basal insulin under the care of their physician. The choice of the post-study basal insulin, and the dose and injection time were at the discretion of the treating physician. It was recommended to adjust the doses of the new basal insulin based on SMPG data. In total (combining the patients in trials EFC11628, EFC11629 and EFC12777), there were 363 patients who were followed after converting from investigational drug to commercial insulin. Of these patients, 182 patients were in the HOE901-U300 arm.

For the purposes of labeling, it is important to understand how insulin doses were converted from the completion of the 12-month study period to the follow up period (for EFC11628 and EFC11629) and the conclusion of the 16-week period (for PDY12777). In order to better understand this change, Dr. Ketterman, the FDA statistician, at my request, calculated the change in insulin doses from the datasets provided by the Sponsor. The results of these calculations are shown in Table 87 and Table 88

After the completion of the 12-month study period, 62% to 95% of all patients were converted to Lantus in all trials; see (Table 89, Table 90, Table 91).

Across all studies, there was a decrease in insulin basal doses upon converting to commercial insulins. In the HOE901-U300 group, this dose decrease ranged between 13.6% to 20.7%. Smaller decreases were seen in the Lantus group (see Table 87).

To capture events related to dose conversion, the reviewer focused on severe hypoglycemia events, hyperglycemia TEAEs and differences in SMPGs within the first week of the follow up period (discussed by individual study below). Any event occurring after one week from the insulin dose conversion was not considered related to the dose conversion.

**Table 87 – Change in insulin doses from the conclusion of the 12-month on-treatment period to the 1<sup>st</sup> week of the follow up period across completed trials EFC11628 and EFC11629**

Study	Change* in <b>basal</b> insulin dose from end of study to week 1 follow up		Change* in Prandial insulin dose from end of study to week 1 follow up		Change* in <b>Total</b> insulin dose from end of study to week 1 follow up	
	(U)	(U/kg)	(U)	(U/kg)	(U)	(U/kg)

EFC11628	<b>HOE901-U300</b>	N=35		N=31		N=31	
	<i>Absolute change:</i> mean(std)	-17.70(28.79)	-0.17(0.26)	0.54(8.06)	0(0.07)	-19.10(28.39)	-0.18(0.26)
	<i>Percent change:</i> mean(std)	-14.76(21.47)	-14.76(21.47)	4.78(38.19)	4.78(39.19)	-10.30(13.88)	-10.30(13.88)
	<b>Lantus</b>	N=25		N=20		N=20	
	<i>Absolute change:</i> mean(std)	-10.87(27.62)	-0.09(0.22)	-2.43(8.30)	-0.01(0.07)	-15.06(32.30)	-0.11(0.26)
	<i>Percent change:</i> mean(std)	-8.86(26.73)	-8.86(26.73)	1.60(21.13)	1.6(21.13)	-6.19(18.66)	-6.19(18.66)
EFC11629	<b>HOE901-U300</b>	N=103					
	<i>Absolute change:</i> mean(std)	-16.37(26.94)	-0.16(0.25)				
	<i>Percent change:</i> mean(std)	-15.18(21.46)	-15.13(21.49)				
	<b>Lantus</b>						
	<i>Absolute change:</i> mean(std)	-2.81(12.45)	-0.03(0.15)				
	<i>Percent change:</i> mean(std)	-3.36(12.57)	-3.36(12.58)				

\*difference between value at week 1 follow-up and baseline follow-up  
Source: Statistics performed by FDA Statistician, at the request of this reviewer.

**Table 88 – PDY12777 - Change in insulin doses from the conclusion of the 16-week study to the 1<sup>st</sup> week of the follow up period**

The MEANS Procedure  
Description of Planned Arm=HOE901-U300 (Evening/Morning)

Label	N	Median	Minimum	Maximum	Mean	Std Dev
Change from Baseline	12	-2.79	-31.00	0.36	-5.50	8.68
Percent Change from Baseline	12	-9.88	-54.39	1.83	-14.44	17.59

Description of Planned Arm=HOE901-U300 (Morning/Evening)

Label	N	Median	Minimum	Maximum	Mean	Std Dev
Change from Baseline	11	-2.36	-6.00	0.50	-2.35	2.45
Percent Change from Baseline	11	-9.24	-21.43	1.96	-8.08	8.22

Description of Planned Arm=Lantus (Evening/Morning)

Label	N	Median	Minimum	Maximum	Mean	Std Dev
Change from Baseline	11	-1.00	-7.14	0.29	-2.33	2.85
Percent Change from Baseline	11	-6.67	-42.02	2.86	-9.68	13.45

Description of Planned Arm=Lantus (Morning/Evening)

Label	N	Median	Minimum	Maximum	Mean	Std Dev
-------	---	--------	---------	---------	------	---------

Label	N	Median	Minimum	Maximum	Mean	Std Dev
Change from Baseline	9	0.00	-5.71	6.00	-0.38	3.12
Percent Change from Baseline	9	0.00	-14.29	16.22	-1.87	8.86

Source: Statistics performed by FDA Statistician, at the request of this reviewer.

### EFC11628

There were a small number of patients evaluated for adverse events during the 4-week follow up period. This small number is due to the introduction of an amendment requiring this follow up, late in the study period. Hence, only 8.3% of the randomized population (67 of 806 patients) was included in this portion of the study. Of these patients, 40 patients were in the post HOE901-U300 group, and 27 were in the post Lantus group. See Table 89 for information regarding follow up treatments selected in this trial.

**Table 89 - Post treatment medications: Anti-diabetic insulinic medications - Number of patients by basal/mealtime insulin category and standardized medication name - 4-week follow-up population – EFC11628**

Insulin category Standardized medication name	Post-HOE901-U300 (N=40)	Post-Lantus (N=27)
Any anti-diabetic insulinic post treatment medications	39 (97.5%)	27 (100%)
Basal	39 (97.5%)	27 (100%)
Insulin glargine	38 (95.0%)	24 (88.9%)
Isophane insulin	1 (2.5%)	3 (11.1%)
Mealtime	38 (95.0%)	26 (96.3%)
Insulin aspart	20 (50.0%)	9 (33.3%)
Insulin lispro	15 (37.5%)	14 (51.9%)
Insulin glulisine	4 (10.0%)	3 (11.1%)

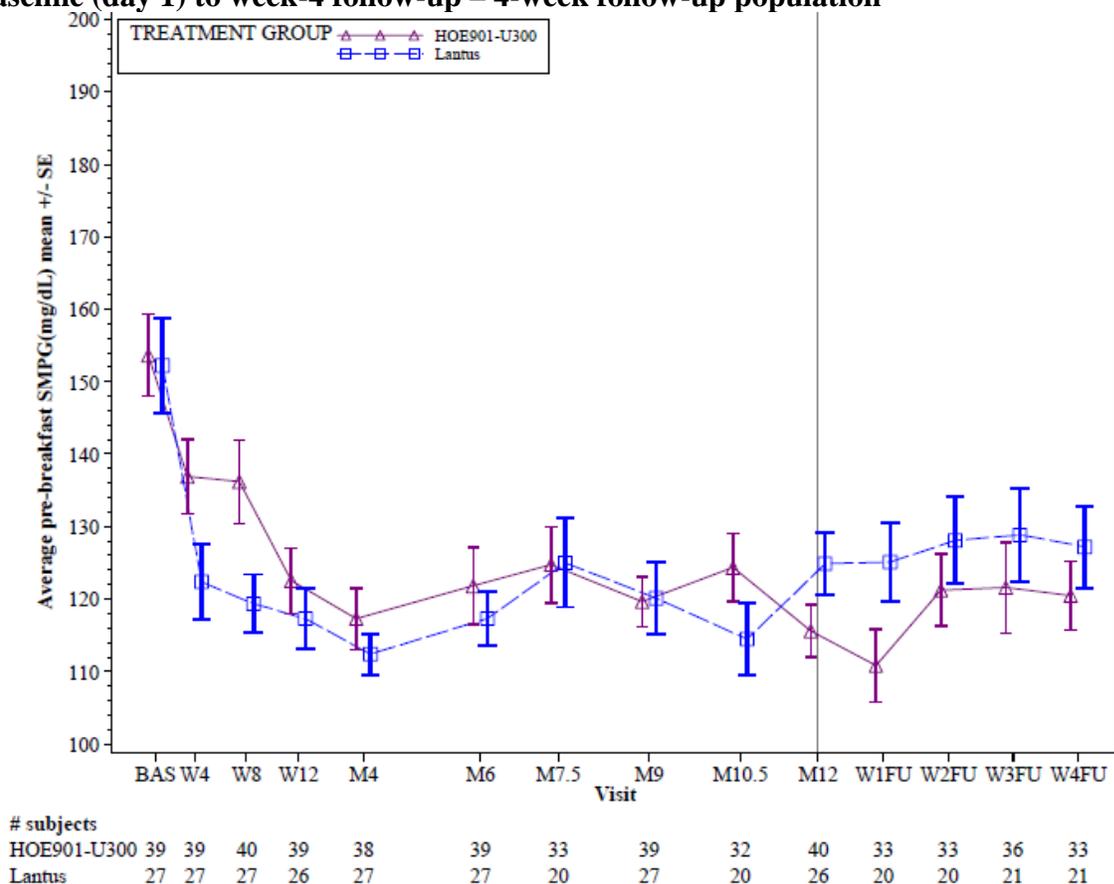
Insulin category was derived applying classification from clinical review WHO-DD dictionary: WHO-DDE 2013 SEPTEMBER 1  
Antidiabetic post treatment medications are those that the patient continued beyond 1 day after last injection of IMP or those the patient started 1 day or later after the last IMP injection until the end of the study.  
Standardized medication name are sorted by decreasing frequency in the treatment group Post-HOE901-U300.  
Source: 120-Day Safety Update Report, Table 1 (page 400)

The majority of patients were converted to Lantus (>88.9% in both groups).

During the first week of the 4-week follow-up period, compared with the last dose of HOE901-U300 or Lantus, average doses of commercial basal insulin were decreased by a mean of 14.76% in patients converted from HOE901-U300 and by 8.86% in patients converted from Lantus. The basal insulin dose levels reached at the end of the first week of the 4-week follow-up period were maintained almost unchanged during the remainder of the 4-week follow-up period (see Table 87).

The average prebreakfast SMPG at the conclusion of the 12-month study period was slightly higher in the Lantus group (HOE901-U300: 115.6 mg/dL vs. 123.7 mg/dL in the Lantus group). At week 1 of the follow-up period, the HOE901-U300 SMPG values remained lower than the Lantus SMPG values.

**Figure 41 – EFC11628 - Mean ( $\pm$ SE) in average prebreakfast SMPG (mg/dL) by visit from baseline (day 1) to week-4 follow-up – 4-week follow-up population**



BAS = Baseline

SMPG=Self Monitoring Plasma Glucose

FU refers to follow-up period

4-week follow-up period begins 2 days after last IMP intake

Average is assessed by the mean SMPG calculated over the 7 days preceding the given visit.

Note: All visits are based on observed cases.

Note: During the 4-week follow-up period, patients from both treatment groups, HOE901-U300 and Lantus, had changed from IMP to a commercial basal insulin

Source 120-Day Safety Update Report, Figure 3

No patients reported severe hypoglycemia during the 4-week follow up period.

**Reviewer’s comments: It is important to interpret the SMPG results in light of the small cohort of patients studied (only 67 patients). Despite the decrease in SMPG values in the HOE901-U300 group, more than the Lantus group; there were no reports of severe**

**hypoglycemia in this study. The 14.8% decrease in basal insulin dose when converting from HOE901-U300 to a commercial insulin, may have decreased the occurrence of severe hypoglycemia in this study.**

EFC11629

The small number of patients enrolled in the 4-week follow-up period was due to a late amendment introducing this period to the study. By the time this amendment was introduced, the majority of patients had already completed the treatment period. A total of 248/811 patients (30.58%) were studied. Of these 116/404 patients (28.7%) were in the post HOE901-U300 group and 132/407 patients (32.4%) were in the post Lantus group.

The majority of patients were converted to insulin glargine (>76% in both groups), see below.

**Table 90 – Post treatment medications: Anti-diabetic insulinic medications - Number of patients by basal/mealtime insulin category and standardized medication name - 4-week follow-up population – EFC11629**

Insulin category Standardized medication name	Post-HOE901-U300 (N=116)	Post-Lantus (N=132)
Any anti-diabetic insulinic post treatment medications	116 (100%)	129 (97.7%)
Basal	114 (98.3%)	128 (97.0%)
Insulin glargine	89 (76.7%)	112 (84.8%)
Isophane insulin	19 (16.4%)	9 (6.8%)
Insulin human injection, isophane	11 (9.5%)	9 (6.8%)
Insulin detemir	2 (1.7%)	1 (0.8%)
Insulin isophane human semisynthetic	1 (0.9%)	0
Mealtime	3 (2.6%)	5 (3.8%)
Insulin glulisine	2 (1.7%)	1 (0.8%)
Insulin aspart	1 (0.9%)	4 (3.0%)
Other	7 (6.0%)	3 (2.3%)
Human mixtard	3 (2.6%)	1 (0.8%)
Insulin	3 (2.6%)	0
Insulin human	1 (0.9%)	2 (1.5%)

Insulin category was derived applying classification from clinical review

WHO-DD dictionary: WHO-DDE 2013 SEPTEMBER 1

Antidiabetic post treatment medications are those that the patient continued beyond 1 day after last injection of IMP or those the patient started 1 day or later after the last IMP injection until the end of the study.

Standardized medication name are sorted by decreasing frequency in the treatment group Post-HOE901-U300.

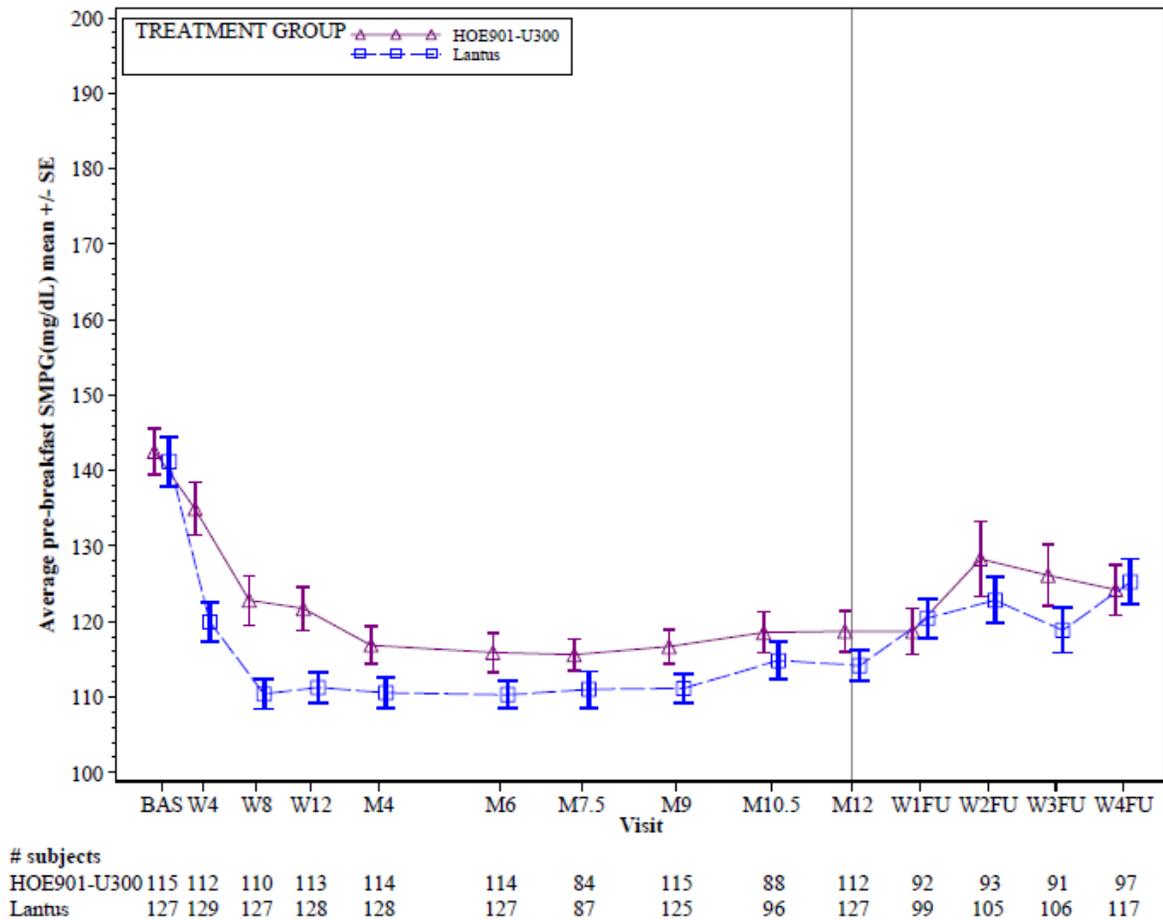
Source 120-Day Safety Update Report, Table 1 (page 415)

During the first week of the 4-week follow-up period, compared with the last dose of HOE901-U300 or Lantus, average doses of commercial basal insulin were decreased by a mean of 15.18% in patients converted from HOE901-U300 and by 3.4% in patients converted from Lantus (see

Table 87). The basal insulin dose levels at the end of the first week of the 4-week follow-up period were maintained almost unchanged during the remainder of the 4-week follow-up period.

The average prebreakfast SMPG at the 4-week follow-up baseline was similar in both groups (HOE901-U300: 119.4 mg/dL vs. 114.4 mg/dL in the Lantus group). At week 1, SMPG values were similar between groups. HOE901-U300 SMPG values increased up to Week 2 compared to the Lantus values.

**Figure 42 - EFC11629 - Mean ( $\pm$ SE) in average prebreakfast SMPG (mg/dL) by visit from baseline (day 1) to week-4 follow-up - 4-week follow-up population**



BAS = Baseline; SMPG=Self Monitoring Plasma Glucose

FU refers to follow-up period

4 week follow up period begins 2 days after last IMP intake

Average is assessed by the mean SMPG calculated over the 7 days preceding the given visit.

Note: All visits are based on observed cases.

Note: All patients from the 4-week follow-up population are taken into account in this graph, whether they received rescue therapy or not

Note: During the 4-week follow-up period, patients from both treatment groups, HOE901-U300 and Lantus, had changed from IMP to a commercial basal insulin

Source 120-Day Safety Update Report, Figure 3

One patient, (011629840142001), in the post HOE901-U300 group, reported severe hypoglycemia during Week 2 of the 4-week follow-up in the post HOE901-U300 group. This patient was converted from 114 units of HOE901-U300 to 80 units of NPH and 4 mg of glimepiride during the follow-up period.

**Reviewer's comment: The report of severe hypoglycemia in a post-HOE901-U300 patient is not likely related to the conversion of insulins, since it occurred beyond 1 week after the insulin dose conversion.**

**Unlike trial EFC11628, where a decline in prebreakfast SMPG values were seen at week 1 of follow up, this study shows an increase in SMPG values.**

#### EFC12777

During the first week of the 4-week follow-up period, compared with the last dose of the HOE901-U300 or Lantus, mean doses of commercial basal insulin were decreased by a mean of 8.08% to 14.44% in patients converted from HOE901-U300 and by 1.87% to 9.68% in patients switched from Lantus (see Table 88). No patients reported severe hypoglycemia during the follow up period.

The majority of patients were converted to insulin glargine (>60% in both groups), see Table 91.

**Table 91 – Number (%) of patients who used post-treatment antidiabetic medications in study PDY12777**

Pharmacological Class Chemical Class Standardized medication name	HOE901-U300	Lantus
	Combined	Combined
	(N=30)	(N=29)
Any antidiabetic post-treatment medications	25 (83.3%)	21 (72.4%)
Insulins and analogues	24 (80.0%)	20 (69.0%)
Insulins and analogues for injection, fast-acting	23 (76.7%)	20 (69.0%)
Insulin lispro	16 (53.3%)	13 (44.8%)
Insulin aspart	6 (20.0%)	7 (24.1%)
Insulin glulisine	2 (6.7%)	0
Insulins and analogues for injection, intermediate-acting	21 (70.0%)	20 (69.0%)
Insulin lispro	16 (53.3%)	13 (44.8%)
Insulin aspart	6 (20.0%)	7 (24.1%)
Insulins and analogues for injection, long-acting	21 (70.0%)	19 (65.5%)
Insulin glargine	20 (66.7%)	18 (62.1%)
Insulin detemir	1 (3.3%)	1 (3.4%)
Insulins and analogues for injection, intermediate-acting combined with fast-acting	16 (53.3%)	13 (44.8%)
Insulin lispro	16 (53.3%)	13 (44.8%)

“combined” refers to Morning then evening group and evening then morning group.  
Source: modified from demo-data 16.2.4.4.6.1

In this trial no planned SMPG during the follow-up period was performed.

### 7.5.2 Time Dependency for Adverse Events

See section 7.3.4 Significant Adverse Events (The time to occurrence of severe hypoglycemia (as reported by investigator))

### 7.5.3 Drug-Demographic Interactions

Exploratory subgroup analyses were performed by the Sponsor to evaluate if there was heterogeneity of treatment effect (HOE901-U300 vs. Lantus) on TEAEs across subgroups:

#### Age

The majority of patients (74% of HOE901-U300 group and 73% of the Lantus group) were younger than 65 years of age. A small number was 75 years of age or older (3% and 4% of the HOE901-U300 and Lantus group respectively). In patients <65 years of age, the incidence of TEAEs in the nervous system disorders SOC was 13.0% in the HOE901-U300 group and 8.6% in the Lantus group, driven mainly by the HLT headaches NEC. In patients ≥65 to <75 years of

age, TEAEs in the musculoskeletal and connective disorders SOC were reported in 10.0% of the HOE901-U300 group and 17.6% of the Lantus group.

Overall, no clinically relevant difference was found in the AE profile between age groups or between age groups and the overall population.

### Sex

Overall, no clinically relevant differences were found in AE profiles between male and female patients or between gender and the overall population. Overall, females reported more TEAEs than male patients did (number of patient reported events of any SOC for women: 685/1187, [57.7%] vs. 696/1301, [53.5%] for males). Most of this difference was made up by SOC of infections and infestations and gastrointestinal disorders.

### Race

As noted in the section 6.1.2 Demographics, the majority of participants (about 88%) were Caucasian. Black patients made up <8% of patients in the T2DM studies. No clear race by drug interaction could be identified by the Sponsor's analysis.

### Others:

There were some demographic groups that were small in numbers, and that comparison of TEAE by patient was thus not clinically meaningful comparisons. These groups included: Ethnicity (82% were non-Hispanic), eGFR<60 (as 83% of patients had an eGFR $\geq$ 60 mL/min/1.73m<sup>2</sup>) and history of hepatic disease (90% of patients had no hepatic disease).

## **7.5.4 Drug-Disease Interactions**

## **7.5.5 Drug-Drug Interactions**

For detailed discussion of drug-disease interactions, see the Clinical Pharmacology review. Insulin glargine is not expected to be directly influenced by other drugs because it is a peptide.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

Please refer to section

7.3.5 Submission Specific Primary Safety Concerns.

### **7.6.2 Human Reproduction and Pregnancy Data**

HOE901-U300 has not been studied during pregnancy and lactation in clinical studies. Non-clinical studies in insulin glargine (100 U/mL) are presented below.

### Nonclinical studies:

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine (100 U/mL) was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36

mg/kg/day, which is approximately 50 times the recommended human SC starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human SC starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, 5 fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development were normal.

Two pregnancies were reported in the development program:

1. Subject ID: 013560276001029 -- Patient participated in Phase 1 program. She received HOE901-U300 without polysorbate (R) in treatment period 1 (first day of administration: (b) (6); last day: (b) (6)). She received insulin glargine U300 with polysorbate (T) in treatment period 2 (first day of administration: 01-JUL-2013; last day: 06-JUL-2013). Patient was found to be pregnant (b) (6). Pregnancy was reported on (b) (6) as an AE with an onset date on Day (b) (6) of the study (b) (6) which was the first day of the last menstrual period. Pregnancy ongoing at the time of dossier cut off
2. Subject ID: 012777840003017 -- Patient participated in Phase 2 program. Patient was randomized to HOE901-U300. Pregnancy, per LMP occurred on day 31 of study. On day 62, the patient had a positive pregnancy test and treatment was discontinued. On follow-up phone call patient confirmed, she delivered a healthy newborn prematurely (at gestational week 32). Infant stayed 21 days in Neonatal intensive care unit due to premature delivery.

**Reviewer's comments: The human pregnancy data in patients on HOE901-U300 is very small. No conclusions can be derived from these few cases. However, there are no concerns.**

### 7.6.3 Pediatrics and Assessment of Effects on Growth

There are no completed pediatric studies available for review of the use of HOE901-U300 in pediatric patients. The Sponsor submitted an initial Pediatric Study Plan (iPSP) to IND 112400. Although HOE901-U300 is a 3X concentrated formulation of Lantus, because the PK/PD profiles of HOE901-U300 are different from the reference drug, Lantus, it was considered a change in the dosing regimen and therefore triggered PREA (Pediatric Research Equity Act). The PerC (Pediatric Review Committee) reviewed the iPSP on 2/5/14.

(b) (4)

The Sponsor submitted a PPSR (Proposed Pediatric Study Request) on 11/26/14, which is being reviewed by the Agency.

#### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Refer to section 7.3.5 Submission Specific Primary Safety Concerns overdose section for further details.

HOE901-U300, as with other insulins, does not have any known mechanisms that could result in an abuse potential. The Sponsor did not identify any trend or pattern in HOE901-U300-treated patients concerning AEs with a potential for drug abuse.

There were no reported adverse events of withdrawal syndrome or rebound reported.

#### **7.7 Additional Submissions:**

The 120-day safety update did not add any new information that changes the general safety assessment of the original NDA. The treatment exposure for HOE901-U300, at the conclusion of the 12-month on-treatment period, in the two completed studies, was 376.7 patient-years (EFC11628) and 369.8 patient-years (EFC11629).

## **8 Postmarket Experience**

## **9 Appendices**

### **9.1 Literature Review/References**

### **9.2 Labeling Recommendations**

Labeling recommendations are contained within this review as appropriate. A line by line labeling review will be conducted separately.

### **9.3 Advisory Committee Meeting**

No advisory committee meeting was convened for this NDA.

## 9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 206538

Submission Date(s): April 25, 2014

Applicant: sanofi-aventis U.S. LLC

Product: insulin glargine [rDNA origin] injection, 300 Units/mL

Reviewer: Tania A. Condarco, MD

Date of Review: January 2015

Covered Clinical Study (Name and/or Number): PDY12777, EFC11628, EFC11629, EFC12347, EFC12456

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 2439 investigators without disclosable interests+ 11 investigators with disclosable financial interests +2 with missing information = total 2452 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>none listed</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>11</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>2</u>		

Clinical Review  
Tania A. Condarco, M.D.  
NDA206538  
Toujeo, insulin glargine [rDNA origin] injection, 300 Units/mL

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Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
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I believe that the Applicant has adequately disclosed the financial interests/arrangements of the clinical investigators. Given the large number of investigators, and the large number of patients studied to support this application, the small number of investigators with disclosable financial interests is unlikely to substantially affect the integrity of the data. Additionally, each of the investigators with disclosable financial interests contributed only small percentage of patients to the studies in which they participated. This further reassures me that their participation is unlikely to affect the integrity of the data or impact the approvability of the application.

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/s/  
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TANIA A CONDARCO  
01/28/2015

LISA B YANOFF  
01/28/2015

## MEMORANDUM

Filing Meeting: June 12, 2014

NDA 206538

Drug: Insulin glargine [rDNA origin] injection, 300 Units/mL; HOE901-U300

Sponsor: Sanofi-Aventis US LLC

Proposed Indication: To improve glycemic control in adults with diabetes mellitus

Clinical Reviewer: Hyon J. Kwon, PharmD, MPH

Date received: April 25, 2014

PDUFA date: February 25, 2015

### Assessment:

From the clinical standpoint, the NDA is fileable.

### Background:

Sanofi-Aventis submitted this NDA for insulin glargine [rDNA origin] injection, 300 Units/mL (HOE901-U300), to be available as a 1.5 mL glass cartridge in a disposable, pre-filled pen injector (SoloStar). Insulin glargine is a recombinant human insulin analog, and is a long-acting parenteral blood glucose-lowering agent.

Insulin glargine 300 U/mL has the same composition as the current commercial formulation of insulin glargine 100 U/mL (Lantus) but with three times the amount of active ingredient and corresponding zinc content in a smaller injection volume. Lantus (insulin glargine injection, 100 Units/mL) was approved on April 20, 2000 for once daily subcutaneous administration to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

(b) (4)

The sponsor evaluated the incidence of nocturnal hypoglycemia as a key secondary endpoint in the Phase 3 studies.

A pre-NDA meeting was held on October 25, 2013, and discussions related to the following clinical issues occurred:

- We expressed concerns (b) (4)
- The sponsor sought agreement (b) (4)

## CLINICAL FILING CHECKLIST FOR NDA

(b) (4)

The overall clinical program includes six Phase 1 clinical studies (PKD10086, PKD11627, PKD12270, PKD13560, PDY12335, and TDR11626), one Phase 2 study (PDY12777), and four pivotal multinational Phase 3 studies (EFC11628, EFC11629, EFC12347, and EFC12456), where a total of 1686 patients received at least one dose of HOE901-U300.

As of October 29, 2013, the cut-off date for the NDA submission, the 6 month treatment period of four Phase 3 studies was complete, but the 6-month extension periods were ongoing. The four pivotal Phase 3 trials included:

Study	Phase	Population		Treatment	No. patients		Status at cutoff date 29 Oct 2013
		Type	Description		Planned	Randomized	
<b>Pivotal studies</b>							
EFC12456	3	T1DM	Patients on basal insulin + mealtime insulin	HOE901-U300 or Lantus, injected once daily in the morning or evening	500	549	Main 6-month on-treatment period (completed), 6-month safety extension (ongoing)
EFC11628	3	T2DM	Patients on basal insulin + mealtime insulin	HOE901-U300 or Lantus, injected once daily in the evening	800	807	Main 6-month on-treatment period (completed), 6-month safety extension (ongoing)
EFC11629	3	T2DM	Patients on basal insulin + OAD	HOE901-U300 or Lantus, injected once daily in the evening	800	811	Main 6-month on-treatment period (completed), 6-month safety extension (ongoing)
EFC12347	3	T2DM	Insulin-naïve patients not adequately controlled with non-insulin AHA	HOE901-U300 or Lantus, injected once daily in the evening	800	878	Main 6-month on-treatment period (completed), 6-month safety extension (ongoing)

In all four pivotal Phase 3 trials, the sponsor assessed the efficacy and safety of HOE901-U300 compared to Lantus in the treatment of adult patients with T1DM and T2DM by evaluating the noninferiority of HOE901-U300 compared to Lantus, based on the mean

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## CLINICAL FILING CHECKLIST FOR NDA

change of HbA1c from baseline to endpoint (at Month 6 as the primary efficacy analysis) with a noninferiority margin of 0.4% HbA1c. The occurrence of nocturnal hypoglycemia was also one of the main secondary efficacy endpoints. Nocturnal hypoglycemia was defined as severe and/or confirmed hypoglycemia by SMPG  $\leq 70$  mg/dL reported between 00:00 and 05:59 hours, from the start of Week 9 to Month 6.

The efficacy and safety of HOE901-U300 when injected at intervals of up to 3 hours earlier or later than patient's usual once daily injection time was evaluated in two 3-month substudies during the extension periods of studies ECF11628 (N=109) and ECF11629 (N=89).

The sponsor also conducted a meta-analysis based on pooled efficacy data from the main 6-month treatment period of studies EFC11629 and EFC12347 (studies with non-insulin AHA as background therapy).

The Pediatric Study Plan (PSP) was previously submitted and agreed-upon (February 18, 2014 submission).

The proposed proprietary name, Toujeo SoloStar, was submitted on April 30, 2014.

Based on discussion with Cynthia Kleppinger from OSI, we selected 6 sites from one T1DM trial (EFC12456) and two T2DM trials (EFC11628 and EFC12347) for inspection. See Clinical Inspection Request Consult dated June 12, 2014 for details.





## CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
					months in Phase 3 studies
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	x			Adverse events coded using the MedDRA version 16.0
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			Sponsor evaluated injection site reactions, hypersensitivity reactions, cancers, cardiovascular events, and hepatic events
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Narratives provided in Section 15.3.3 of each individual study report
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			Yes from clinical standpoint – sponsor submitted lab with both SI and US conventional units
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Sponsor submitted agreed-upon PSP
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	Insulin glargine does not have abuse potential
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			To be confirmed by stats
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			To be confirmed by stats - sponsor also provided lab parameters in US unit
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			To be confirmed by stats
37.	Are all datasets to support the critical safety analyses	x			To be confirmed by

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

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## CLINICAL FILING CHECKLIST FOR NDA

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

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_ YES \_\_**

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

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

**None at this time**

Hyon J Kwon, PharmD, MPH

\_\_\_\_\_  
Reviewing Medical Officer

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Date

Lisa Yanoff, MD

\_\_\_\_\_  
Clinical Team Leader

\_\_\_\_\_  
Date

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/s/  
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HYON J KWON  
06/13/2014

LISA B YANOFF  
06/13/2014