CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206538Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MDCM
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	206538
Applicant Name	Sanofi-Aventis
Date of Submission	April 25th 2014
PDUFA Goal Date	February 25th 2015
Proprietary Name / **Established (USAN) Name**	Toujeo (insulin glargine injection)
Dosage Forms / Strength	Sterile solution for subcutaneous injection The strength is 1800 nmol of insulin glargine per mL The potency is 300 U of insulin glargine per mL (U-300)
Proposed Indication(s)	1. To improve glycemic control in adults with diabetes mellitus
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tania Condarco, MD
Statistical Review	Anna Kettermann, PhD
Pharmacology Toxicology Review	Jeffrey Quinn, PhD
CMC Review/OBP Review	Xavier Ysern, PhD
Microbiology Review	Neal Sweeney, PhD
Clinical Pharmacology Review	Lau Sze, PhD
DDMAC	Ankur Kalola, Pharm D
DSI	Kleppinger Cynthia, MD
CDTL Review	Yanoff Lisa, MD
OSE/DMEPA	Vee Sarah, Pharm D
OSE/DRISK	Vega Amarilys, MD
Other/CDRH	McGowan, Ryan, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

On April 25, 2014 Sanofi-Aventis submitted a new drug application for Toujeo under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.

Toujeo is a sterile solution containing 300 units of insulin glargine per mL. Sanofi-aventis also owns and markets Lantus, a sterile solution containing 100 units of insulin glargine per mL (NDA# 21081).

The applicant is seeking to indicate Toujeo to improve glycemic control in adults with diabetes mellitus. Toujeo is a drug-device combination product. The presentation is a disposable pen, with an irreversibly integrated 1.5 mL cartridge pre-filled with a sterile drug product solution. The drug product is to be administered once daily by subcutaneous injection and the dose is to be individualized according to the individual's metabolic needs, blood glucose monitoring results, and glycemic control goal.

Toujeo will be the second concentrated insulin (i.e., insulin with a potency of > 100 units/mL) available on the US market. The other concentrated insulin is a vial presentation of a 5-fold concentrated solution of regular insulin [Humulin R (U500)]. Concentrated insulins may be useful for insulin resistant patients requiring large amounts of insulin per day (i.e., >200 units) because they obviate the need for delivering a large insulin dose[1] by way of two or more injections.

Medication and dosing errors resulting in serious unintended consequences (i.e., severe hypoglycemia from unintentional overdose) have been a major problem with the Humulin R (U500) vial presentation (NDA#18780). These errors stem in part from the fact that no dedicated devices are available to administer the insulin leaving patients and caregivers with the burden of performing volumetric conversions to calculate dose. Dosing errors are expected to be less of an issue with Toujeo because the presentation is not in vial form, the delivery device is specifically designed to deliver the U300 formulation and no dose calculation/volumetric conversion is required for dosing and administration. Furthermore, the cartridge is irreversibly integrated in the pen device and cannot be easily removed from the device. This will further limit the possibility of dosing errors arising from administration with insulin syringes calibrated for 100 units/mL products.

[1] Note: The current Toujeo device can only administer a maximum of 80 units at a time.

Concentrated insulins, owing to slower systemic absorption, have distinct pharmacodynamic properties which in some case may more closely approximate basal physiologic pancreatic insulin secretion and result in improved glycemic control.

2. Background

Drs. Yanoff and Condarco have summarized the regulatory history for the application (refer to Section 2 of their respective reviews). In brief, the applicant had initially proposed to qualify the new glargine dosage strength by demonstrating bioequivalence (BE) between Toujeo (insulin glargine, 300 units/mL) and Lantus (insulin glargine, 100 units/mL) and the Division agreed with this approach. The BE study demonstrated that the two formulations were not bioequivalent. The applicant, encouraged by the product PK/PD profile, proposed to establish the safety and effectiveness of the new dosage strength in four pivotal trials. The intent of these trials was to; first establish glycemic non-inferiority to Lantus, then glycemic superiority to Lantus (referred to as a "second" primary endpoint), then superiority on a hypoglycemia related endpoint[2]. There was no disagreements regarding the primary efficacy objective (demonstration of change in HbA1c non-inferiority) or proposed trial designs to reach this objective. Areas of discussions and disagreements focused mostly on the adequacy of proposed secondary endpoints to address the third objective (b) (4) The detailed interactions and advice given to the applicant by Division on this topic are described in Dr. Condarco's review.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer, Dr. Ysern, regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 30 months between 2 °C and 8 °C protected from light for unopened product and expiry of (b) (4) days at room temperature (up to 30 °C) protected from light for opened (i.e., in use) product. There are no outstanding issues related to CMC, device engineering or human factors/usability (refer to Dr. Yanoff's CDTL summary for details). Particularly, the human factors study demonstrated that 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).

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by, Dr. Quinn, the pharmacology/toxicology reviewer that there are no outstanding pharmacology toxicology issues that preclude approval. The toxicology data submitted for the approval of Lantus (insulin glargine, 100 U/mL) support the

[2] Refer to page 44 of the Statistical Analysis Plans for Studies EFC11628 and EFC11629

approval of Toujeo. A local tolerance study was conducted to bridge Toujeo to Lantus. Toujeo and Lantus displayed similar local tolerability in rabbits following subcutaneous injection.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Refer to Dr. Lau's and Yanoff's reviews for details. PK/PD data support a recommendation for once daily administration. Toujeo compared to Lantus has a longer terminal half-life[3] and greater intra-individual variability[4]. The glucose lowering effect of Toujeo begins to wane approximately 30 hours after injection compared to 26 hours for Lantus (refer to Figure 5 in Dr. Yanoff's review), suggesting Toujeo is slightly longer lasting than Lantus. Although greater intra-individual variability raises concerns with regard to day-to-day performance-reproducibility and the impact this may have on glycemic control (i.e., risks of highs and low glucose), Phase 3 clinical trial data did not reveal any major or concerning differences between the two insulins on glycemic control (i.e., adverse reactions related to hyper or hypoglycemia) at the end of 26-weeks (refer to Dr. Condarco's review).

The major clinical pharmacology issue identified in the clinical pharmacology review was a lack of unit-to-unit (i.e., dose-to-dose) potency (i.e., glucose lowering effect) equivalence between Toujeo and Lantus. Single dose and steady state clinical pharmacology studies revealed that, on a unit-to-unit basis, Toujeo has less glucose lowering effect than Lantus. Table 7 in Dr. Lau's review compares the maximum (GIR_{max})[5] and overall glucose lowering effects (GIR-AUC)[6] of Toujeo relative to Lantus when equivalent doses [0.4 units per kilogram (U/kg)] of the two drugs are administered once daily for eight days to patients with type 1 diabetes. The maximum glucose lowering effect achieved with Toujeo was ~ 19% lower than that of Lantus and the overall glucose lowering in the 24 and 36 hours that followed the injection was also lower relative to Lantus by 27% and 15% respectively.

[3] 19 versus 13 hours for Toujeo versus Lantus
[4] Maximum and overall glucose lowering variability based on a coefficient of variation comparison is 2-fold higher in Toujeo versus Lantus
[5] Glucose infusion rate maximum (GIR max)
[6] Area under the glucose infusion rate (GIR-AUC)

Table 1 –Ratio[7] of GIR between U300 and U100 in Multiple-Dose PK/PD Study TDR11626

Parameter	Estimate	90% CI	95% CI
GIR_{max}	0.81	0.68 – 0.97	0.65 – 1.01
$GIR\text{-}AUC_{0\text{-}24}$	0.73	0.56 – 0.94	0.53 – 0.99
$GIR\text{-}AUC_{0\text{-}36}$	0.85	0.70 – 1.03	0.67 – 1.08

Source: modified from Dr. Lau's Table 7

The decrease in *in vivo* potency between Toujeo and Lantus was attributable to the fact that a lower systemic glargine exposure was achieved when 0.4 units per kg of Toujeo were administered compared to when 0.4 units per kg of Lantus were administered (refer to Figure 3 in Dr. Yanoff's CDTL).

The glargine insulin and zinc concentration are the only differences between the Toujeo and Lantus product formulations (both are 3-fold higher in Toujeo). Dr. Tran (CMC team lead) postulates that the observed PK/PD differences result from differences in systemic absorption of glargine from the subcutaneous tissue. Insulin glargine is insoluble at neutral pH and forms a precipitate (e.g., hexamers of glargine) when injected in the subcutaneous tissue. Glargine in its precipitated form cannot readily cross capillary membranes which limits its systemic absorption. The higher glargine protein concentration in Toujeo is expected to increase the tendency for subcutaneous precipitation and to limit the amount of glargine available for systemic absorption.

The impact of the PK/PD differences were noted in Phase 3 clinical trial data where, across each of the four pivotal clinical trials in both type 1 and type 2 diabetes, it was observed that subjects randomized to Toujeo required between 12 to 19% more units of insulin to achieve a similar level of glucose control (refer to Table 12 in Dr. Condarco's review).

(b) (4)

In pivotal trials, the applicant relied on a one-to-one conversion to switch patients from pre-trial basal insulin to Toujeo and from pre-trial basal insulin to Lantus (see Table 6 in Dr. Condarco's review) and, at the beginning of the trial, unit doses of insulin were similar and balanced between the two arms (refer to Table 12 in Dr. Condarco's review). In addition, titration algorithms used within each trial did not account for potency differences between Toujeo and Lantus (see Table 8 in Dr. Condarco's review). In the early part of each of the four trials, when baseline doses of insulin in units per kg in the Toujeo and Lantus arms were equivalent, the hypoglycemia comparison was biased in favor of Toujeo because the applicant failed to account for potency differences between the two insulins at the time of randomization. In essence the rates of hypoglycemia reflect a comparison between a less effective insulin (Toujeo) and a more effective insulin (Lantus). In this setting it is likely that hypoglycemia differences are predominantly driven by dose differences (the arm that is underdosed will have less hypoglycemia) rather than by some other product specific

[7] Toujeo (0.4 U/kg) divided by Lantus (0.4 U/kg)

difference (i.e., the flatter and longer steady state PK profile). It is likely that lowering the dose of Lantus to match the lower effectiveness of Toujeo would have achieved the same salutary effect on hypoglycemia rate. This will be discussed further in the Section 6 and 7 of this memorandum.

The Office of Clinical Pharmacology raised several questions with regards to the observation of the lack of *in vivo* unit-to-unit potency equivalence between Toujeo and Lantus. They did not agree with the applicant's proposal (b) (4)

The CMC and clinical teams did not agree (b) (4) From a CMC perspective, the strength (nmoles/mL) and potency (U/mL) of Toujeo was adequately characterized. One unit of insulin glargine is defined as the activity contained in 36.4 mcg of glargine (6 nmoles) per the European Pharmacopeia standard. To establish the potency of Toujeo, the mass (mg) amount of insulin glargine in Toujeo was measured by chromatography and converted to units using the European Pharmacopeia insulin glargine standard. The applicant, using the same batch of Toujeo, compared the chromatography derived potency to potency derived using a bioassay and confirmed that both strength (1800 nmoles/mL) and potency (300 U/mL) were preserved for Toujeo.

From a clinical perspective, the lack of unit-to-unit PD equivalence between Toujeo and Lantus could potentially lead to worsening glycemic control when converting from Lantus to Toujeo and better glycemic control when converting from Toujeo to Lantus in the care setting. The risk of the former was evaluated in clinical trials. In the early part of the trials, night time glycemic control (using fasting pre-breakfast SMBG as a surrogate) was worst on Toujeo than on Lantus but no serious hyperglycemia related issues (i.e., DKA or hyperosmolar hyperglycemia coma) were identified for either patients with type 1 or type 2 diabetes mellitus. In these trials, the lower Toujeo effectiveness was eventually overcome by using higher doses of Toujeo as reflected by the end of the trial Toujeo dose which was 12-19% higher than Lantus dose. Titration of Toujeo will occur in the care setting as doses of all insulins are individualized to target patient specific goals. Care givers will be instructed to monitor glucose frequently in the first month after Toujeo is initiated to minimize the risk of hyperglycemia while transitioning to Toujeo. The risk of slightly worst glycemic control when switching from one insulin to the next is a potential issue with currently marketed basal insulins (i.e., NPH, glargine, detemir).

In the care setting, converting from Toujeo to Lantus could potentially lead to an increase in glucose lowering of approximately of 10-20%[8] placing patients at increased risk for hypoglycemia. Switching between insulin preparations in the care setting should be done only under close supervision because it is widely recognized that each insulin preparation has slightly different PK/PD characteristics. The risk of hypoglycemia in this setting is labeled for all insulin products. The clinical team felt that the risks of hyper and hypoglycemia specific to the fact that this product shares an active ingredient with an already labeled product but has distinct pharmacodynamics could be adequately mitigated through Sections 2 (Dosage and Administration), 5 (Warning and Precautions) and 12 (Clinical Pharmacology) of the product label.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Details of the trial design and analyses can be found in Dr. Condarco's and Kettermann's reviews. Dr. Yanoff has also summarized efficacy results in her CDTL memorandum. No efficacy issues that preclude approval were identified in the reviews.

The applicant relies on four clinical trials to support the indication. The four pivotal trials were randomized, open-label, parallel group, trials comparing Toujeo to Lantus across the following patient populations and clinical use scenarios.

- **Trial EFC12456:** Patients with type 1 diabetes inadequately controlled on multiple daily insulin injections (i.e., basal/bolus insulin therapy switch study)
- **Trial EFC11628**: Patients with type 2 diabetes inadequately controlled on multiple daily insulin injections (i.e., basal/bolus insulin therapy switch study)
- **Trial EFC11629:** Patient with type 2 diabetes inadequately controlled on basal insulin injections in combination with oral antidiabetic therapies (basal insulin therapy switch study)
- **Trial EFC12347:** Patients on with type 2 diabetes inadequately controlled on oral anti-diabetic medications (add-on to oral anti-diabetic in insulin naïve patient study)

[8] To provide context on the magnitude of this doses increase; a 10% dose increase was recommended for patients not optimally controlled on their dose of basal insulin in the type 1 DM clinical trial Trial#12456. In the care setting it would not be uncommon for a physician to increase insulin dose by 10% for patients not optimized on their current insulin regimen.

The primary objective for each trial was to demonstrate that the change in Hemoglobin A1c from baseline to Week 26 in the Toujeo arm was not worse than the change in Hemoglobin A1c from baseline to Week 26 in the Lantus arm by a difference of 0.4% or more (i.e., non-inferiority comparison with a non-inferiority margin set at 0.4%).

In the three 'switch' studies, patients transitioned from their pre-trial basal insulin dose to the intervention insulin dose using the same scheme[9] for both Lantus and Toujeo. In the add-on to oral anti-diabetic drug trial, patients were initiated on a 0.2 units/kg dose of either Toujeo or Lantus. At randomization, baseline insulin dose in units/kg were identical across intervention groups (i.e., Lantus and Toujeo) for each of the four trials[10]. The trials employed a basal insulin (i.e., Lantus and Toujeo) titration scheme targeting a pre-breakfast self-monitored glucose between 80 to 130 mg/dL in the type 1 diabetes trial and 80 to 100 mg/dL in the type 2 diabetes. Dose increases in basal insulin could occur no more frequently than every 3-4 days. The dosing scheme (initial dose and titration) which, at randomization, assumed that the two insulins are equally effective on a unit-to-unit basis impacts interpretation of the hypoglycemia data. This is discussed in Section 5 and 7 of this memorandum.

Across all trials, baseline demographics and disease characteristics were balanced and no major issues in study design or execution that would impact primary efficacy analyses or interpretation were identified. The primary analysis was based on a modified intent to treat population. To handle data missing at 26 weeks, the applicant relied on both a Last Observation Carried Forward (LOCF) strategy and on a Mixed Model Repeated Measures (MMRM) strategy. Although Dr. Kettermann points to inadequacies in both of these methodologies with regard to estimating the true value of the data missing at 26 weeks, she was reassured by the relatively small amount of data missing and the consistency across results obtained using the two imputation methods. She concludes that missing data is not a primary decisive factor in this application.

Dr. Yanoff has summarized the main efficacy findings and results of analyses using two missing data imputation methods in Table 2 of her CDTL memorandum. This table is reproduced below for convenience. Across all four studies, Toujeo was found to offer a level of HbA1c control that was non-inferior to that of Lantus after 26 weeks of treatment. Subgroup analyses did not reveal significant interactions across regions, baseline demographic or disease characteristics.

[9] Refer to Table 6 in Dr. Condarco's review.
[10] Refer to Table 12 in Dr. Condarco's review.

Table 1: Main Efficacy Findings in The Four Toujeo Pivotal Trials (from Dr. Yanoff's review)

Study	Treatment group	N	Baseline Mean	Endpoint Mean	Change from baseline	
					LS Mean	LS Mean difference (95% CI)
Type 1 Diabetes						
EFC12456 T1DM basal-bolus	Toujeo	273	8.13	7.70	-0.40	0.05 (-0.08, 0.18)* 0.04 (-0.10, 0.18)^
	Lantus	273	8.12	7.68	-0.44	
Type 2 Diabetes						
EFC11628 T2DM basal-bolus	Toujeo	404	8.14	7.25	-0.83	-0.002 (-0.11, 0.11)* -0.02 (-0.13, 0.09)^
	Lantus	400	8.14	7.28	-0.83	
EFC11629 T2DM basal + OADs	Toujeo	403	8.28	7.57	-0.57	-0.01 (-0.14, 0.12)* -0.02 (-0.15, 0.11)^
	Lantus	405	8.22	7.56	-0.56	
EFC12347 T2DM insulin naive	Toujeo	432	8.49	7.08	-1.42	0.019 (-0.12, 0.16)* 0.04 (-0.09, 0.17)^
	Lantus	430	8.58	7.05	-1.46	
Source: adapted from primary reviews *LOCF method ^MMRM method						

Glycemic control, and specifically nighttime glucose control, was not equivalent for the entire trial duration. Indeed, the average fasting pre-breakfast glucose value (i.e., fasting morning SMBG), a reflection of both nighttime glucose control and basal insulin effectiveness, was worst on Toujeo compared to Lantus in the first half of each of the four trials. This is shown in the following figures which graph mean fasting pre-breakfast SMBG values across each visit in the Toujeo (purple triangles) and Lantus (blue squares) arms.

Figure 1: Pre-breakfast SMBG by Visit; Type 1 Diabetes EFC12456-Basal Bolus Trial

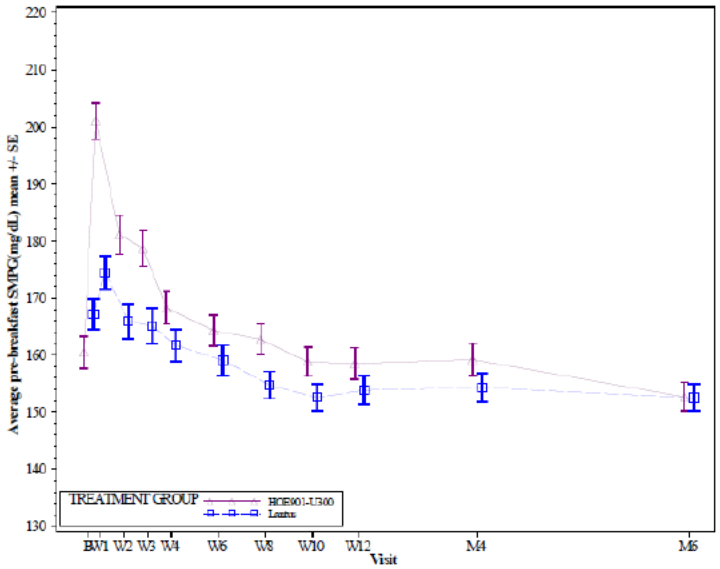


Figure 2: Pre-breakfast SMBG by Visit; Type 2 Diabetes TEFC11628-Basal Bolus Trial

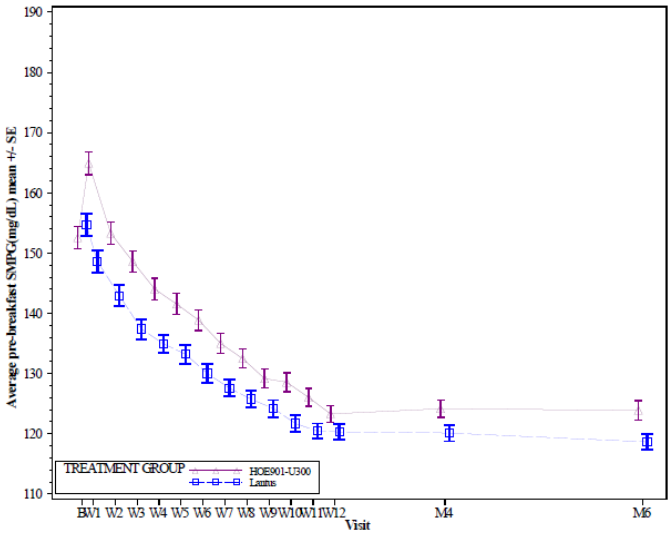


Figure 3: Pre-breakfast SMBG by visit; Type 2 Diabetes EFC11629-Basal add-on to OAD Trial

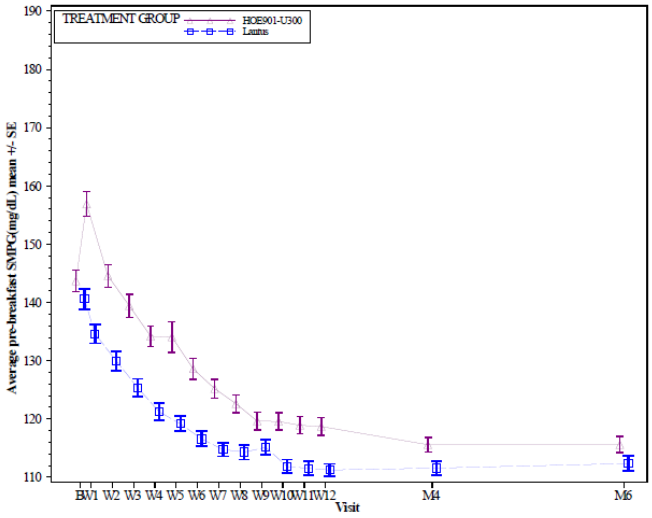
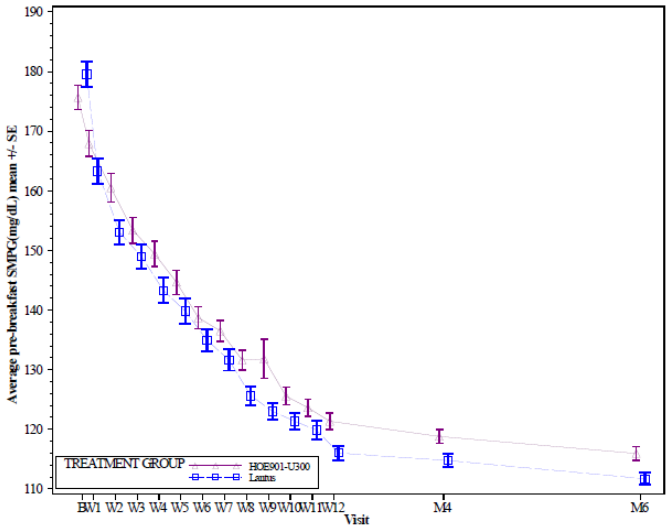


Figure 4: Pre-breakfast SMBG by visit; Type 2 Diabetes EFC12347-Basal add-on to OAD Trial



This differential effectiveness in the early part of the trial was corroborated by the observation of a consistently larger magnitude of dose increase in the Toujeo arm for each study visit in each of the four trials. Recall that the titration algorithm was similar between arms and differential dose increase was driven entirely by differences in fasting morning SMBG (Refer to figures 11, 17, 23, and 29 in Dr. Condarco's review for graphs of consecutive dose increase by visit in each of the four trials).

The differential unit-to-unit effectiveness of the two insulins was eventually overcome with differential dose titration [both basal and and when applicable bolus insulin) and did not result in large HbA1c differences at Week-26. Recall that HbA1c is a "weighted" average of blood glucose levels for the 120 days that precede the test. It is a "weighted" average because glucose levels in the 30 days preceding the test contribute substantially more to the level of HbA1c than do glucose levels between days 90 to 120. This may partly explain why the level of glucose control can be different early in the trial and still be roughly similar at trial end in a 26 week trial.

Another reason could be that similarities in glucose control in the daytime (~3/4 of the hours in a 24 hour period) mask differences in nighttime effectiveness (~1/4 of the hours in a 24 hour period) and that HbA1c is insufficiently sensitive to detect these differences. The applicant points to 24 hour average self-measured blood glucose (point-of-care derived) profiles to claim that overall no difference in SMBG reported glycemic control was observed across seven consecutive time points in the trial. Two trials show a trend towards numerically worst control on Toujeo across all time points (ECF12456 and ECF12347)[11] and two trials show differences in a few early and late time points (i.e., Week 2 and 4; ECF11628 and ECF11629)[12] also suggesting numerically worst control on Toujeo. These analyses are less granular than the Pre-Breakfast SMBG analyses (i.e., fewer time points considered) and real

[11] Refer to figures 12 and 30 in Dr. Condarco's review
[12] Refer to figures 19 and 24 in Dr. Condarco's review

differences in nighttime effectiveness (i.e., ascertained by two time points; 3 AM and pre-breakfast) for a part of the day could be masked by the more numerous time points obtained during waking hours (i.e., post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner, bedtime).

8. Safety

Drs. Yanoff and Condarco have summarized the main safety findings in the application. The main safety database comprised of 304 and 1242 patients with type 1 and type 2 diabetes respectively exposed to Toujeo. The median exposure duration was 183 days in both groups. Seventy six and 89 percent of patients with type 1 and 2 diabetes were exposed for at least 25 weeks respectively. The total exposure at 6 months is consistent with the FDA draft guidance for products to treat diabetes mellitus. Although there is relatively sparse 1-year data the active ingredient is not a new molecular entity and the exposure number and duration were judged to be sufficient for filing. No new concerning safety signal that would preclude approval was identified in the safety analyses. I agree with Dr. Yanoff's summary of the main safety findings which are repeated below in italics.

"Notable findings from these safety assessments include:

- *Injection site reactions and Hypersensitivity reactions were relatively balanced between treatment groups and generally consistent with current Lantus labeling. The incidence of injection site reactions is shown below. The most common preferred terms were 'injection site bruising' and 'injection site pain'. There were no serious reactions.*

	T1DM		*T2DM*	
	Toujeo	*Lantus*	*Toujeo*	*Lantus*
Any injection site reaction	*2.6%*	*1.6%*	*2.4%*	*3.1%*

- *There was no apparent imbalance in CV risk although the incidence of any MACE event was only about 1% or less in both treatment groups.*
- *There were no reported accidental 'overdose' of U300 due to misunderstanding of the concentration of the formulation*
- *There were two reports of 'hyperglycemia' during the first week of randomized therapy – one in each treatment group suggesting no clinically important implications of the lesser PD effect of U300 within this early time frame. There were no reports of diabetic ketoacidosis (DKA) or severe hyperglycemia.*
- *There were no important differences in body weight between Toujeo and Lantus treated patients.*

<u>Common Adverse Events</u>:

Common adverse events were comparable between Toujeo and Lantus. The only adverse events (other than hypoglycemia) reported with a frequency ≥5% and more commonly with Toujeo were nasopharyngitis and upper respiratory tract infection. These are unlikely to be related to insulin use.

	T1DM		*T2DM*	
	Toujeo	*Lantus*	*Toujeo*	*Lantus*
Nasopharyngitis	*12.8%*	*10.9%*	*7.1%*	*5.8%*
Upper respiratory tract infection	*9.5%*	*7.6%*	*5.7%*	*5.4%*

Other Safety Analyses:
All other routine safety analyses such as laboratory findings, vital signs, electrocardiograms were reviewed by Dr. Condarco and found to be unremarkable.

In addition, the difference in insulin effectiveness noted in Section 7 may impact risks of hyperglycemia and hypoglycemia while transitioning to or from Toujeo. Risks may be amplified in the care setting as compared to the clinical trial setting because monitoring will be less frequent. Labeling will be used to emphasize the fact that Toujeo and Lantus products have distinct pharmacokinetics that could impact effectiveness during transition if wrong assumptions are made. Instructions to physicians in the Dosing and Administration, Warnings and Precautions, and Clinical Pharmacology Sections of the full prescribing information will be used to minimize this risk.

Hypoglycemia in the Toujeo Program

Too few patients experienced at least one event of severe hypoglycemia (i.e., third party assistance required for recovery) across the four trials to draw meaningful conclusions from these analyses and no unexpected large imbalance in any arm or trial was observed (the two basal bolus trials had the highest risk as expected). Dr. Yanoff in Table 5 of her CDTL shows that larger numerical differences in the proportion of patients experiencing at least one episode of severe hypoglycemia were observed in the early part of the trial when glycemic control, and particularly nighttime glycemic control, was worst on Toujeo.

In the type 1 diabetes trial a similar proportion of patients experienced at least one episode of hypoglycemia across multiple definitions of hypoglycemia which; aim to capture less-severe hypoglycemic episodes and differ in their diagnostic sensitivity/specificity (See Table 48 in Dr. Condarco's review). Across the three type 2 diabetes trials, numerically fewer patients experienced at least one episode of these less-severe hypoglycemia episodes (refer to Tables 51, 53, and 55 in Dr. Condarco's review). Analyses that split the trial timeline into Week 0 to 8 and Week 9 to 24 reveal that the greatest numerical difference between Toujeo and Lantus is observed between Week 0 to 8 when glycemic control was worst on Toujeo (refer to Tables 52 and 54 in Dr. Condarco's review). These analyses are consistent with lead time analyses performed by Dr. Kettermann and shown in Table 13 of her review.

Hypoglycemia analyses for the entire trial duration that take into account level of glycemic control by comparing the proportions of patients who; achieve a threshold level of control (i.e., HbA1c <7.0%) and have no events of hypoglycemia (severe and a less-severe definition) show no differences or trends between groups (refer to Tables 25, 29, 33 and 37 in Dr. Condarco's review).

The applicant sought (b) (4) to make a claim (b) (4) These analyses were regarded as flawed and (b) (4) were viewed as misleading and not supported by substantial evidence.

The main reason why these were regarded as flawed are (b) (4) The applicant, (b) (4) insinuated that the data supported a conclusion (b) (4) This is also a flawed argument. Again, to arrive at this conclusion the applicant should have (b) (4) and this was not done.

(b) (4) We do not believe that the applicant's claim (b) (4) is supported by substantial evidence for the reasons discussed above. (b) (4)

[13] Note per the original multiplicity adjustment strategy in the statistical analysis plan (Refer to page 44 of the Statistical Analysis Plans for Studies EFC11628 and EFC11629) these p-values were not significant.

(b) (4) The Division believes that (b) (4) would be misleading as it is unsubstantiated by substantial evidence.

(b) (4)

9. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

10. Pediatrics

This product does not trigger PREA because it does not involve a new active ingredient, new indication, route of administration, dosage form, or dosing regimen. See Dr. Yanoff's review for additional details.

11. Other Relevant Regulatory Issues

No issues were identified, refer to Drs. Yanoff and Condarco's reviews for details.

12. Labeling

Dr. Yanoff has summarized labeling issues in her CDTL memorandum and I have summarized issues (b) (4) in Section 7 of this memorandum.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The applicant established the efficacy and safety of Toujeo in patients with Type 1 and Type 2 diabetes mellitus across several, relevant, clinical use scenarios. Toujeo administered once daily and titrated to goal resulted in levels of HbA1c reduction which were non-inferior to those observed in Lantus at the end of 26-weeks. The safety of Toujeo was not clinically meaningfully different than the safety of the approved product Lantus. PK/PD characterization revealed that less glargine insulin is systemically absorbed when it is administered as Toujeo compared to Lantus and that Toujeo has less glucose lowering effect on a unit-to-unit basis compared to Lantus. Risks of hypoglycemia, hyperglycemia, and inadequate insulinization when transitioning to or from Toujeo have been discussed in Section 5 of this memo and addressed in specific sections of product labeling. Issues related to real or potential overdose associated with confusion stemming from differences in strengths between Toujeo (1800 nmol/mL) and Lantus (600 nmol/mL) were not observed in clinical trials or Human Factor studies. Strength (insulin potency) will be clearly labeled. The fact that a dedicated device, which is not easily tampered with, is used for product administration mitigates this risk as well. We did not agree with the applicant's conclusion that the data in the application provide conclusive evidence that Toujeo is comparatively safer than Lantus from a hypoglycemia risk perspective. This issue is discussed in Section 5, 6, and 7 of this memorandum.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No new safety findings from this clinical development program prompt the need for a postmarketing risk evaluation and management strategies.

- Recommendation for other Postmarketing Requirements and Commitments

No new safety findings from this clinical development program prompt the need for a postmarketing requirements and commitments.

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/s/

JEAN-MARC P GUETTIER
02/25/2015