NCT Number: NCT02542631

Document Date: 21-Sep-2015

REVIEW AND APPROVAL

Function	Reviewer	Signature/Date
Originator	Vivien Zraick, MS	Vivien Zraick Digitally signed by Vivien Zraick DN: c=US, o=JNJ, ou=Employees, ou=426270, cn=Vivien Zraick, email=VZRAICK@ITS.JNJ.com Reason: I attest to the accuracy and integrity of this document. Date: 2015.09.21 14:51:49 -07'00' Adobe Acrobat version: 11.0.10
Clinical Affairs	Darlene Dreon, DrPH	Darlene Dreon Digitally signed by Darlene Dreon DN: c=US, o=JNJ, ou=Employees, ou=426209, cn=Darlene Dreon, email=DDREON@ITS.JNJ.com Reason: I am approving this document. Date: 2015.09.21 15:22:28 -07'00'
Clinical and Medical Affairs	Ramachandra G. Naik, MD	Ramachandra Naik Digitally signed by Ramachandra Naik DN: c=US, o=JNJ, ou=Employees, ou=1043374, cn=Ramachandra Naik, email=rnaik@ITS.JNJ.com Reason: I am approving this document. Date: 2015.09.21 18:47:02 -04'00'

STUDY PROTOCOL AND STATISTICAL ANALYSIS

Title of Study	Glycemic Control and Treatment Satisfaction Using Finesse Versus Pen for Initiating Bolus Insulin Dosing in Patients with Type 2 Diabetes Mellitus (T2DM) not Achieving Glycemic Targets on Basal Insulin With/Without Anti-Hyperglycemic Agents (AHA)
Devices	• Finesse Bolus Insulin Delivery System cleared for commercialization in United States (US), Europe (EU), and Canada • FlexPen® (aspart) • SoloStar® Pen (glargine)
Study Purpose	In order to enable the Healthcare Provider (HCP) to more easily advance patients with T2DM sub-optimally controlled on basal insulin therapy to basal and bolus therapy, a novel bolus insulin patch ("Finesse") was developed by the Sponsor. The proposed study aims to determine whether initiating and managing bolus therapy with Finesse will result in non-inferior or improved glycemic control in patients with T2DM compared with a pen.

Study Objectives	<u>Primary Objective:</u> To compare the change in A1C, with bolus insulin dosing with Finesse versus pen, from baseline to the completion of 24 weeks of basal and bolus insulin therapy. <u>Secondary Objectives</u>: • To compare the change in other parameters of glycemic control with bolus insulin dosing with Finesse versus pen, from baseline to the completion of 24 weeks and 44 weeks of basal and bolus insulin therapy. • To demonstrate that patient reported outcomes (PRO) improve with Finesse versus pen following the completion of 24 weeks and 44 weeks of basal and bolus insulin therapy. • To demonstrate that HCPs prefer Finesse to pen for initiation of bolus insulin therapy following the completion of 24 weeks of basal and bolus insulin therapy by the last patient at their investigative site.

	• To demonstrate the durability of effect of using Finesse and pen on maintenance of A1C from week 24 to week 44 of basal and bolus insulin therapy. • To demonstrate that patients prefer Finesse to pen for bolus insulin therapy following a 4-week crossover from week 44 to week 48.
Study Design	A randomized, open-label, 2-arm parallel study comparing glycemic control, patient satisfaction, and quality of life (QOL) of using Finesse versus pen to initiate and manage bolus insulin dosing in 312 patients, male and female, ages 22 to 75 years of age with T2DM not achieving glycemic targets on basal insulin with/without AHA. After a 4-week screening/baseline period, patients will be randomized 1:1 (balanced by study center) to either the Finesse arm or the pen arm to initiate bolus insulin using a simple bolus dosing algorithm and followed for a 44-week intervention period. After the final endpoint evaluation at week 44, patients will crossover to the alternate bolus insulin delivery device for 4 weeks and complete a patient preference survey at week 48. The study will be conducted in the following periods: Screening Visit 1 (Week -4 to -3); Baseline Visit 2A (Week -2); Randomization Visit 3 (Week 0) to include insulin dosage optimization;[i,1] Phone Calls Insulin Titration (Weeks 1, 2, 3, 6, 8); Follow-up Visits 4 (Week 4), 5 (Week 12), 6C (Week 24), 7 (Week 36), 8 (Week 44), and 9 (Week 48). Visits 2B (Week -1), 6A (Week 22), and 6B (Week 23): Only the subset of patients performing continuous glucose monitoring (CGM) (50 patients per arm) will have additional visits for performing blinded CGM assessments.
Study Sites	A multicenter study (approximately 50 sites). Sites and patients will be approximately divided between the US and EU.
Patient Population	A total of approximately 312 enrolled adults, male and female, aged 22-75 years, body mass index of ≤ 40 kg/m^2, with T2DM not achieving glycemic targets (A1C 7.5-11.0%)

[i] Educational materials specifically designed for this study based on the International Diabetes Center simple algorithm for adjustment of insulin in Type 2 diabetes. Patients will record SMBG before meals and bedtime, and insulin doses.

	using basal insulin (≥ 0.3 U/kg/day) with/without AHA based on the participant's medical needs.
Duration of Patient Participation	Total duration of participation by each patient is expected to be approximately 52 weeks.
Dosage and Administration	At randomization, total daily dose (TDD) of insulin will be divided as 50:50, basal: bolus (Note: For those subjects with a screening A1C of <9%, the TDD is to be reduced by 10% prior to splitting the dose 50:50, basal: bolus, in order to avoid potential for hypoglycemia at institution of new regimen). Basal insulin therapy for each group will be titrated using a simple algorithm by chart to adjust by 2U increments to achieve pre-morning meal fasting plasma glucose (FPG) target of 71-130 mg/dl (4.0-7.2 mmol/l). Bolus insulin dosing will start with fixed pre-meal doses (divided equally between morning meal, midday meal, and evening meal).[2] Prandial insulin therapy for each group will be titrated using a simple algorithm by chart to adjust by 2U increments based on pre-midday meal and pre-evening meal self-monitoring blood glucose (SMBG) target of 71-130 mg/dl (4.0-7.2 mmol/l) and bedtime SMBG target of 71-130 mg/dl (4.0-7.2 mmol/l): pre-morning meal dose will be titrated based on pre-midday meal SMBG; pre-midday meal dose will be titrated based on pre-evening meal SMBG; pre-evening meal dose will be titrated based on bedtime SMBG. For basal insulin, all patients will use Lantus® (Glargine) by a pen (SoloStar®) before evening meal or at bedtime. For bolus insulin, patients will use Finesse containing rapid-acting NovoLog®/NovoRapid® (Aspart) or the FlexPen®. Patients will discontinue the following AHA: Sulfonylureas, Meglitinides, GLP-1 agonists, bromocriptine, and DPP-4 inhibitors that have not been studied in combination with insulin, namely, saxagliptin and linagliptin. Patients on the following AHAs will continue them in their current doses: Biguanides, Alpha-glucosidase inhibitors, SGLT2 inhibitors, Thiazolidinediones, and DPP-4 inhibitors that have been studied and approved for use in combination with insulin, namely, sitagliptin, alogliptin, and vildagliptin.
Endpoint Evaluation at Week 24	
Primary Endpoint	Change in A1C from baseline to week 24, comparing Finesse versus Pen.
Secondary Endpoints	• Proportion of patients with A1C ≤ 7.0% at week 24;

	• Change in percent of glucose values of CGM measurements (in a subset of patients) within targeted range of 71 and 180 mg/dl (4.0 and 10.0 mmol/l) from a one or two week period of week -2 to week 0 (baseline) to a one or two week period of week 22 to week 24; • Change in 3-day average 7-point SMBG from baseline to week 24; • Change in 3-day coefficient of variation (CV) of 7-point SMBG from baseline to week 24;
Tertiary Endpoints	• Change in A1C from baseline to week 12; • Change in average glucose values of CGM measurements (in a subset of patients) from a one or two week period of week -2 to week 0 (baseline) to a one or two week period of week 22 to week 24. • Change in percent of glucose values of CGM measurements (in a subset of patients) ≤ 70 mg/dl (≤3.9 mmol/l) and percent of values >180 mg/dl (>10.0 mmol/l) from a one or two week period of week -2 to week 0 (baseline) to a one or two week period of week 22 to week 24; • Change in FPG from baseline to week 24; • Change in 3-day insulin doses (total daily dose, basal dose, bolus dose) from baseline to week 24.
Patient Reported Outcomes	• Change in treatment satisfaction for insulin delivery from baseline to week 24; • Change in patient quality of life from baseline to week 24; • Patient experience survey at week 24; • Patient insulin usage survey at week 12 and 24.
Healthcare Provider Reported Outcomes	• HCP experience survey at week 24.
Endpoint Evaluation at Week 44	
Secondary Endpoints	• Change in A1C from baseline to week 44; • Proportion of patients with A1C ≤ 7.0% at week 44; • Change in 3-day average 7-point SMBG from baseline to week 44; • Change in A1C from week 24 to week 44.
Tertiary Endpoints	• Change in A1C from baseline to week 36; • Change in 3-day CV of 7-point SMBG from baseline to week 44. • Change in FPG from baseline to week 44;

	• Change in 3-day insulin doses (total daily dose, basal dose, bolus dose) from baseline to week 44.
Patient Reported Outcomes	• Patient experience survey at week 44; • Patient insulin usage survey at week 36 and 44.
Endpoint Evaluation at Week 48	
Patient Reported Outcomes	• Patient preference survey at week 48.
Safety Observations	• Incidence and rate of severe hypoglycemia[ii,3] • Incidence and rate of non-severe hypoglycemia (≤70 mg/dl) (≤3.9 mmol/l) (both symptomatic and asymptomatic); • Incidence of all adverse events; • Incidence of serious adverse events; • Incidence of adverse device effects; • Incidence of serious adverse device effects; • Discontinuation rate due to adverse events. • Incidence of clinically important changes in clinical laboratory tests, vital signs (pulse, blood pressure), physical examination, and body weight.
Data Analysis	<u>Analysis Sets</u> The intent-to-treat (ITT) analysis set includes all patients who initiated bolus insulin therapy. The modified intent-to-treat (mITT) analysis set includes all the ITT patients who had a baseline and at least one post-baseline A1C measurement. The per protocol (PP) analysis set consists of all mITT patients who complete the 24-week efficacy phase, and have no major protocol deviations that may affect the interpretation of the primary efficacy endpoint. Efficacy measurements will be summarized for both mITT and PP analysis sets; the primary efficacy analyses will be based on the mITT analysis set. The ITT set will be used for all safety analyses. <u>Sample Size Determination</u>

[ii] Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer carbohydrate (including IV dextrose), glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

	The sample size determination is based on the primary endpoint, A1C change from baseline to Week 24. Assuming that the true mean difference in A1C change (Finesse vs Pen) is -0.1% with a SD 1.2%, a study population of 250 completers (125 per arm) is required to achieve a power of 90% for non-inferiority with a margin of 0.4%, i.e., the upper bound 2-sided 95% confidence interval of the difference in mean A1C change (Finesse vs Pen) is less than 0.4%. Assuming a discontinuation rate of 20% (for the 24 week primary endpoint analysis), the number of patients to be enrolled = 250/(1-0.20) = 312 patients (156 per arm). <u>Efficacy Analysis Plan</u> Differences between arms (Finesse arm versus pen arm) at week 24 will be analyzed using analysis of covariance (ANCOVA) model with the baseline A1C value as the covariate; the 2-sided 95% confidence interval of the difference will be computed using the model. The non-inferiority of Finesse to pen will be concluded if the upper bound of the 95% 2-sided confidence interval for change in A1C is less than the inferiority margin of 0.4%. This test is the same as a 1-sided test with an alpha of 0.025. Superiority of Finesse will be tested if non-inferiority is shown. Each of the secondary and tertiary endpoints at week 24 and week 44 will be tested for superiority of the Finesse arm to the pen arm, but the tests will be interpreted inferentially only if non-inferiority is demonstrated with respect to the primary endpoint. Otherwise, the p-values and 95% confidence intervals for the secondary and tertiary endpoints will be considered to be nominal. The continuous endpoints will be analyzed using the same ANCOVA model described for the primary endpoint. The categorical endpoints will be analyzed using a Cochran-Mantel-Haenszel test. The Type 1 error rate will be at 0.05. To evaluate durability of effect of using Finesse versus pen, change in A1C from 24 week to 44 week will be analyzed by treatment groups using t-test for each treatment arm.

	Other general considerations for the statistical analysis will include descriptive statistics (sample size, mean, SD, median, minimum, and maximum) for continuous variables and 95% CI of the mean, and, where appropriate, the percentage values for categorical variables, and tests of significance between treatment arms including p-value and 95% CI. <u>Additional Analyses</u> Analyses will also be performed to examine the relationships between variables known to be associated. In particular, the relationship between A1C and severe hypoglycemia[iii], the relationship between A1C and weight change, and the relationship between A1C and adherence measures will be described in each group. These analyses will be descriptive, primarily using categorical cross-classifications to examine whether any shifts in hypoglycemia, weight change, or adherence measures are consistent with expected changes due to improved glycemic control.

[iii] Severe hypoglycemia is defined as an event requiring the assistance of another person to actively administer carbohydrate (including IV dextrose), glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

[1] Handelsman Y, Mechanick JI, Blonde L, et al. American association of clinical endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. *Endocrine Practice* 17:287-302, 2011.

[2] Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B; PREFER Study Group. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab* 11:45-52, 2009.

[3] American Diabetes Association Work Group on Hypoglycemia. Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 28:1245-1249, 2005.