Comfort-in™ needle free soft injector system

510 K application (K120687)
Sections 20:
Performance Testing: Clinical

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Objective

The purpose of this section is to summarize the available clinical data for the Comfort-in™ Needle-free Injection System to determine if the device is safe and effective for its intended use.

Introduction

As an alternative to the uses of syringes, needle-free jet injectors were developed in 1940s and were implemented for inoculations primarily by the military (1). In recent decades, safe and effective jet injection technologies have gained momentum and proved to be useful in multiple clinical areas. For instance, jet injectors have been used for heparin administration (2), insulin injection (3), delivery of pain medications (4), and even for in vivo gene introduction for gene therapy (5).

The Comfort-in™ Needle-free Soft Injection System has been currently approved and marketed in Korea, Europe and Canada. The Manufacturer has also applied for the US FDA clearance. The device utilizes mechanical spring power to propel 0.1 ml to 0.5 ml of liquid medication through 0.006 inch orifice under a pressure of 4100 psi. The system has sufficient force to pass through the skin and enter the subcutaneous tissue to a depth equivalent to delivery via standard needle syringe. The device uses a low cost, single use disposable syringe called a nozzle. Filling of the nozzle is performed through a vial adaptor but is otherwise identical to drawing liquid medication into a conventional syringe.

Post-Marketing Clinical Experience

Mika Medical Co., a manufacturer of the Comfort-in™ needle-free injection system, has been reviewing all Customer Complains and Feedback in Korea, Canada and Europe.

Since the introduction of the Comfort-in in July 2011, three thousands starter sets have been sold to the Korean Diabetes Care clinics and one thousand eight hundred sets were bought by the esthetic mini-hospitals throughout Korea. Up to date there have been no deaths and/or serious injuries reported, no product recalls or Field Corrective Actions.

A review of all available information showed no malfunction or deterioration in the performance profile of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the serious injuries or death or to a serious deterioration in user's state of health.

Appendix 1 enclosed at the end of this Section describes several clinical cases reported by the Korean physicians in respect to Comfort-in™ clinical use for diabetic patients with severe needle phobia as well as for injecting other medications for esthetic purposes.

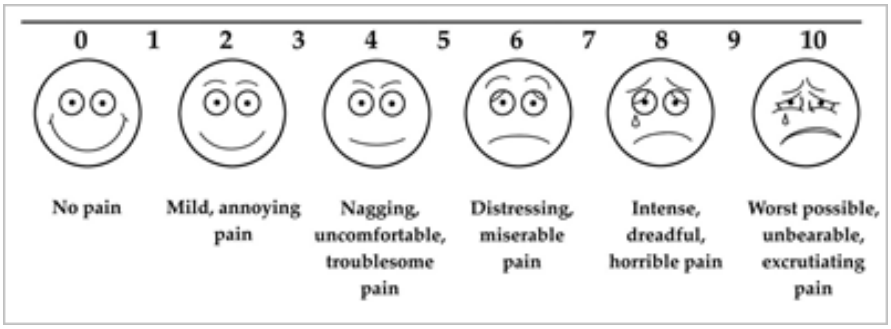
In addition, to comply with the FDA request and in attempt to extend the use of the Comfort-in™ System for insulin injection use, Mika Medical Co. has sponsored an open label cross-over study to compare the pharmacological profile of administration of rapid acting insulin by the Comfort-in™ System to that by FlexPen®.

The study has started on September 17th 2012. Results of the study are expected by the end of January 2013. Synopsis of the Study is outlined in the Table below.

Study Title	An Open Label Crossover Study in Healthy Volunteers to Compare the Pharmacological Profile of Administered Rapid-Acting Insulin by the Comfort-in™ Needle-Free Injector to that by FlexPen®
Short Title	Comparative Study of the Comfort-in™ to the Conventional Insulin Pen
Study Location	Yonsei Severance Hospital, Republic of Korea
Test Product	• The Comfort-in™ (mechanical spring powered needle-free jet injector, manufactured by Mika Medical Co.) **Reference Product:** • The FlexPen® (pen type injector, manufactured by Novo Nordisk)
Objectives	Primary Objectives • To compare pharmacokinetics and pharmacodynamics of subcutaneously injected rapid-acting insulin by the Comfort-in™ needle-free injector to that of administration by FlexPen® • To assess the safety and effectiveness of the Comfort-in™ Device Secondary Objectives • To assess pain and comfort levels of the injection procedures and overall impression of each type of injection
Study Design	This study is conducted as a double-blind, double-dummy, randomized cross-over study in healthy volunteers. Thirty seven (37) healthy volunteers will undergo two euglycemic glucose clamp procedures to ensure data in at least 33 at the end of the clinical study (assuming 10% dropout rate). Subjects withdrawn due to a drug related adverse event or other reasons will not be replaced. Each subject receives the following administration: • The study starts at 08:30 h after an overnight fast and having abstained from smoking, alcohol use and caffeine use for at least

	24 h • Participants in supine position in a temperature controlled room (23°±1°C) • Two catheters are inserted intravenously. • One catheter is inserted in retrograde manner in a dorsal hand vein for blood sampling. This hand is placed in a heated box and kept at 55°C to arterialize venous blood. • The other catheter is placed in an antecubital vein of the contralateral arm for administration of 20% dextrose • After setting up instrumentation a 30 minutes equilibration period is included before blood is sampled for baseline values of the plasma insulin and plasma glucose • Subsequently, all participants receive the rapid-acting insulin injected subcutaneously in the abdomen • On one occasion insulin or placebo is administered by the Comfort-in™; on the other occasion insulin or placebo is administered by the FlexPen® • After administration of insulin plasma glucose is maintained at euglycemic levels (~5.0 mml/L) for 8 hours by a variable infusion of 20% dextrose, the rate by which is determined by plasma glucose measurements at 5-min intervals during the first 4 h and at 10-min intervals thereafter. There will be a minimum washout of 7 days to ensure ten half-lives of insulin between the test periods.
Number of subjects	37 healthy subjects aged 20-50 years old are participating to ensure data in at least 33 at the end of the clinical study. Subjects withdrawn due to a drug related adverse effects will not be replaced.
Study Period	Subjects are dosed in a single cohort group, requiring a total of two study periods. Day 0 is defined as the day prior to first day of dosing (Day 1) in each period. Subjects are admitted to the clinical research unit at 21:00 hours on the evening prior to drug administration and are remained on site until the collection of the last pharmacokinetic sample on Day.
Main criteria for inclusion	• Otherwise healthy subjects who is able to give a written consent • Age 20-50 • Body Mass Index (BMI) of 17-32.5 kg/m2;
Main criteria for exclusion	Standard for Phase 1 PK study in healthy subjects • Evidence or history of clinically significant abnormalities • Have baseline orthostatic hypotension • Positive drug screen, excessive alcohol and tobacco use • Pregnant or lactating women, or who refuse to use contraceptives

	during the study period • Inability to understand the procedure
Drug Administration	Subjects receive an insulin injection by the test product and/or reference device at approximately 9 am in a non-randomized manner • Period 1 fasted (Reference Product) • Period 2 fasted (Test Product)
Plasma PK Sampling	Blood samples for plasma insulin levels are sampled every 10 min during the first hour and every 30 min for the remainder of the study. All PK/PD study endpoints are derived from the exogenous glucose infusion rate (GIR) and insulin concentration profiles.
Safety assessments	Vital signs, hematology, clinical chemistry, urinalysis and electrocardiogram will be performed at Screening and the post-study medical. Subjects will be tested for HepB/C/HIV at screening. Where pre-dose/ admission safety assessments are required: it is assumed that the pre-dose samples are baseline samples only i.e. that the results of these tests are not required before dosing. If this assumption is incorrect, then the admission time will need to be moved earlier on Day -1 to allow time for the results to be returned. On each return admission to the clinical research unit subjects will be tested for drugs of abuse, breathe alcohol and breathe carbon monoxide. Additional safety assessments may be recommended by the Principal Investigator. Advert events (AEs) are monitored throughout the study. Any AEs occurring within 7 days of cessation of treatment (including temporary cessations) are counted as treatment-emergent. Events that occurred in a non-treatment period (for example, washout or Follow-up) are counted as treatment-emergent and attributed to the previous treatment taken.
PK analysis and Statistical Assessments	Non-compartmental analysis of the pharmacokinetic data using industry standard software T lag T max C max AUC to last measured time point (AUC_{last}) AUC to infinity (AUC_{∞}) % AUC extrapolated beyond last measured time point

	Precision of the estimate of PK parameters will be determined by constructing 90% confidence intervals (CIs) around the estimated difference between the Test (Comfort-in™) and Reference (FlexPen®) product using a mixed effects model based on natural log transformed data. Natural log transformed AUC ∞, AUC $_{last}$ and C max will be analyzed using a mixed effect model where sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test/Reference) and corresponding 90% CI will be obtained from the model. The adjusted mean differences and 90% CI for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI. Residuals from the model will be examined for normality and the presence of outliners via visual inspection of plots of residuals versus predicted values and normal probability plots residuals.
Pain and Comfort Evaluations	A brief questionnaire will be completed by the subjects approximately 10-15 minutes post dose. The purpose of this questionnaire is to assess the pain and comfort and overall impression of the injection procedure. This questionnaire will is designed to be administered by a nurse and required 1-2 minutes to complete. The results of the taste questionnaire are reported separately and no formal analysis is required as this information is of exploratory nature. Visual Analog Scale used for the study: 
Primary Study End-Point	• The time to maximal GIR (T-GIR max) – the time until the maximal glucose-lowering effect of insulin is observed
Secondary Outcome Measures	• The maximal GIR (C-GIR max) • The time to 50% of glucose disposal (T-GIR 50%) • The total amount of glucose administered calculated from the area under the curve (AUC) (GIR tot) • T-INS max – the time to maximal insulin concentration • C-INS max – themaximal insulin concentration • The area under the insulin concentration curve (INS AUC) • The time until 50% of insulin absorption, calculated as 50% of the

	area under the insulin concentration curve

References

1. Hoke CH, Jr., Egan JE, Sjogren MH, Sanchez J, DeFraites RF, MacArthy PO, et al. Administration of hepatitis A vaccine to a military population by needle and jet injector and with hepatitis B vaccine. J Infect Dis. 1995 Mar;171 Suppl 1:S53-60.
2. Baer CL, Bennett WM, Folwick DA, Erickson RS. Effectiveness of a jet injection system in administering morphine and heparin to healthy adults. Am J Crit Care. 1996 Jan;5(1):42-8.
3. Wollmer P, Pieber TR, Gall MA, Brunton S. Delivering needle-free insulin using AERx iDMS (insulin diabetes management system) technology. Diabetes Technol Ther. 2007 Jun;9 Suppl 1:S57-64.
4. Bennett J, Nichols F, Rosenblum M, Condry J. Subcutaneous administration of midazolam: a comparison of the Bioject jet injector with the conventional syringe and needle. J Oral Maxillofac Surg. 1998 Nov;56(11):1249-54.
5. Sawamura D, Ina S, Itai K, Meng X, Kon A, Tamai K, et al. In vivo gene introduction into keratinocytes using jet injection. Gene Ther. 1999 Oct;6(10):1785-7.

APPENDIX 1

CLINICAL CASE STUDIES REPORTS