BD Protocol #: **DBC-17NUCLS07**

Protocol Title: **Nucleus Claims Study: Evaluating the User Performance and Experience of Nucleus Pen vs. Commercially Available Pen Needle**

Current Version	Version 5.0 December 20, 2017 (Amendment 4)
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Sponsor Medical Monitor	Laurence Hirsch, Worldwide Vice President, Medical Affairs BD Diabetes Care Office #: 201-847-6518 Mobile #: 908-715-9159
Sponsor Risk Assessment	☐ Significant Risk (SR) ☒ Non-significant Risk (NSR) ☐ Minimal Risk

This study will be performed in accordance with all stipulations of the protocol and in compliance with all applicable BD Policies and Procedures. This study will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and the Belmont Report. Study conduct will comply with US FDA Regulations, applicable state and local regulations, and the Good Clinical Practice guidelines set forth by the International Conference on Harmonization (ICH-E6) and ISO14155.

SPONSOR PROTOCOL APPROVAL

Signature below indicates approval of the protocol as written.			
Individual or function	**Name**	**Signature**	**Date**
Medical Affairs Team Representative	Shahista Whooley	*This document is signed electronically in the eTMF system*	
Medical Monitor	Laurence Hirsch, MD	*This document is signed electronically in the eTMF system*	
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INVESTIGATOR SIGNATURE PAGE

Principal Investigator	
Investigational Site	

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in compliance with all applicable Good Clinical Practices and regulations.

_____ _____

Signature of Principal Investigator Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AUC	Area Under Curve
BD	Becton, Dickinson and Company
BG	Blood Glucose
BMI	Body Mass Index
cat	Catalog
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report/Record Form
DFSP	Defective or Failed Study Product
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
GCP	Good Clinical Practice
G	Gauge
HIPAA	Health Insurance Portability and Accountability Act
HCP	Healthcare Practitioner
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
INJ	Injection
IRB/EC	Institutional or Independent Review Board/Ethics Committee
lbf	Injection Peak Forces
mm	Millimeter
NDC	National Drug Code
NI	Non-inferiority
PHI	Protected Health Information
PI	Principal Investigator
PN	Pen Needle
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

1.0 INTRODUCTION

From a market research study (Van Gogh; 2013) – the results showed that User's perception could not differentiate BD pen needles from other competitors. Therefore, the pen needle market is currently being driven primarily by cost. This study will be used to support the business replacement strategy for BD's current 4mm pen needle. A design improvement is being implemented by introducing a flatter hub (base) by eliminating the post on the hub. This study is designed to assess the User's experience and preference and outcomes are intended to be used for marketing claims. This study will have four study groups based on commercially available 32G pen needle groups: 1) BD Nano, 2) NovoFine, 3) NovoFine Plus & NovoTwist and 4) Other 32G (such as UltiMed, MHC, or other private label).

2.0 OBJECTIVES

2.1 **Primary Objectives**

For all study groups combined, compare user preference for the BD Nucleus pen needle vs. current commercially available pen needles.

2.2 **Secondary Objectives**

For each individual study group, compare user preference for the BD Nucleus pen needle vs. current commercially available pen needles.

For all study groups combined and each individual study group, compare the user experience with the BD Nucleus pen needle and the commercially available pen needles for component preference.

a. Outer Cover Handling
b. Inner Shield Handling
c. Hub Comfort

For all study groups combined and each individual study group, compare the user experience with the BD Nucleus pen needle and the commercially available pen needles for the following:

a. Overall Comfort
b. Anxiety Associated with a Needle Stick Injury
c. Injection Pain
d. Bruising
e. Bending
f. Ease of Use
g. Leakage from this injection site

2.3 **Exploratory Objectives**

For all study groups combined, assess the user acceptance for the following items for the pen needle (non-comparative):

a. Teardrop Label Removal Force
b. Outer Cover Removal Force
c. Inner Shield Removal Force
d. Ease of Insulin Delivery

In addition, Pen Needle breakage will be monitored (all groups combined).

A sub-group with Asian ethnicity, all study groups combined, will also be evaluated for the objectives listed in the Primary and Secondary Objectives.

3.0 STUDY DESIGN

3.1 Overall Study Design

This is a multi-site, prospective, open-label, randomized, 2-period crossover (15 days per period) study comparing commercially available 32G pen needles to the BD Nucleus pen needle. Nucleus pen needle will be compared to four *groups* of pen needles: 1) BD Nano (32Gx4mm), 2) NovoFine (32Gx6mm), 3) NovoFine Plus (32Gx4mm) & NovoTwist (32Gx5mm) and 4) Other 32G (such as UltiMed, MHC, or other private label). Approximately 25% of the subjects are expected to be Type 1 patients and the remaining 75% are expected to be Type 2 patients.

The study is targeting 260 subjects. A total of 240 evaluable subjects are needed with an additional 20 subjects for subjects lost to follow up or other significant protocol deviations. Each group will consist of approximately 60 subjects. Each subject will be screened to determine eligibility into the study. Subjects entering the study who are currently injecting with one of the above mentioned pen needles will automatically be enrolled in their respective group. For example, if a subject comes in using the BD Nano, they will be enrolled in Group 1. If their current pen needle group has completed enrollment, they will be eligible for wash-in (see below).

To facilitate recruitment, a 14 day wash-in period will be allowed in the following situations:

- As BD holds the vast majority of the Pen needle market share in the US, enrolling subjects using non BD brands will be difficult. Subject's currently using a 32G pen needle of 4, 5 or 6 mm lengths will be allowed to wash-in if their current pen needle group has completed enrollment of 60 evaluable subjects. These subjects will be eligible to wash-in to the next available applicable group, per the Wash-In randomization schedule. The length of their current pen needle will be maintained.
- For subject's currently using a 31G pen needle of 4, 5 or 6 mm lengths provided the subject is willing to switch to an assigned commercially available 32G pen needle for the duration of the study. These subjects will be eligible to wash-in to an available applicable group, per the Wash-In randomization schedule. The length of their current pen needle will be maintained.

  Wash-in subjects will be randomized as follows:
  - If subject is currently on a 31G x 4mm or 32G x 4mm they will get randomized to either Group 3 (Novo Fine Plus (32Gx4mm) or Group 4 (UltiCare Micro 32Gx4mm).
  - If subject is currently on a 31G x 5mm or 32G x 5mm, they will randomized to either Group 3 (NovoTwist (32Gx5mm)) or Group 4 (MHC Easy Touch 5mm x 32G).
  - If subject is currently on a 31G x 6mm or 32G x 6mm, they will randomized to either Group 2 (Novo Fine (32Gx6mm)) or Group 4 (Simple Diagnostics Comfort EZ 6mm x 32G).

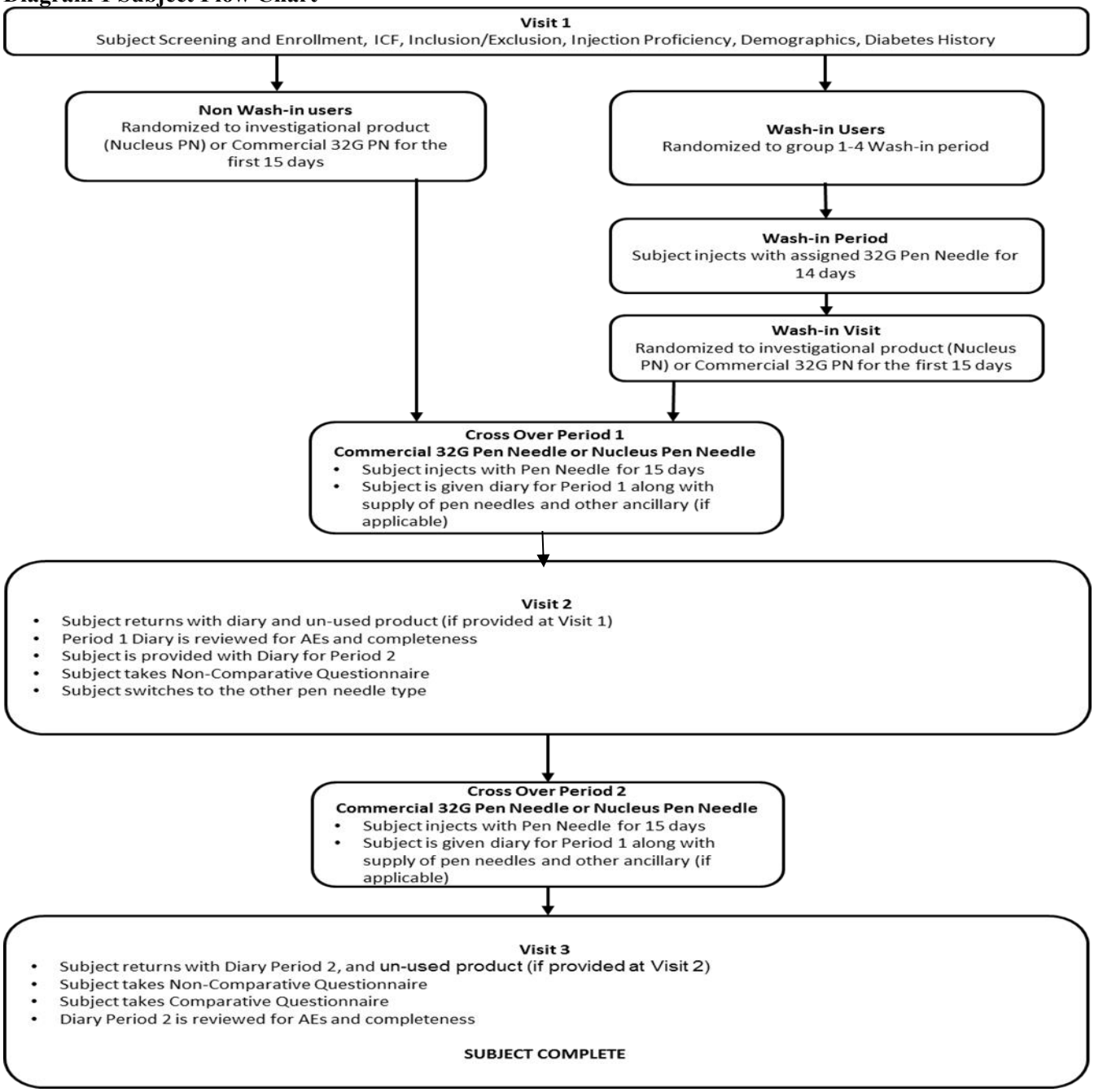
  Please refer to the Wash-in randomization schedule.

Subjects who will remain on their current 32G pen needle will be required to visit the site a total of three times. Wash-in subjects will have an additional visit (Wash-in Visit) for a total of 4 visits. (see Subject Flow Chart Diagram 1).

The study will consist of two 15 day periods (+/- 3 days, no fewer than 13 days and no more than 17 days) in which the subject will use each pen needle (BD Nucleus pen needle or Commercially available 32G pen needle, order randomized) for injection.

Results will be compared to address the Primary, Secondary and Exploratory objectives. A final report will be issued summarizing all outcomes and conclusions.

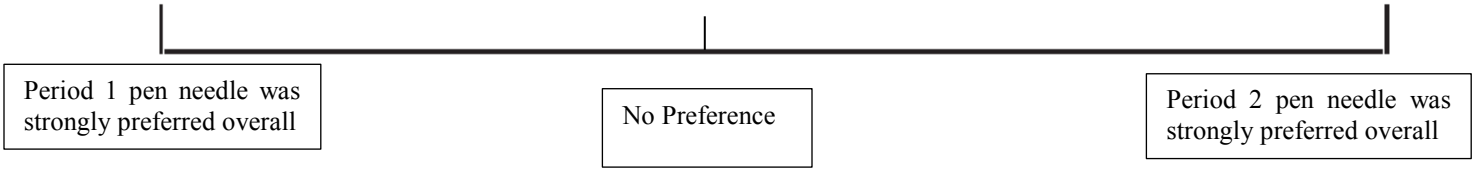
Diagram 1 Subject Flow Chart



3.2 Specification of Study Endpoints

3.2.1 Primary Endpoints

Preference: At the end of the last study period, each subject will be asked to evaluate his or her perception using a 150mm relative VAS scale. The question "Which pen needle did you prefer overall?" will be asked. The far left (-75mm) of the scale will be labelled "Period 1 pen needle was *strongly* preferred overall". The 0mm center point will be labelled "No Preference". The far right (+75mm) of the scale will be labelled "Period 2 pen needle was *strongly* preferred overall".



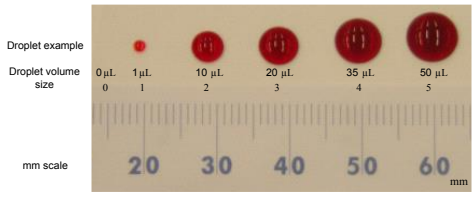
3.2.2 Secondary Endpoints

At the end of the last study period: Each subject will be asked to evaluate his or her perception using a 150mm relative VAS scale for each of the following endpoints: Overall Comfort, Anxiety Associated with a Needle Stick Injury, Injection Pain, and Ease of Use.

After each injection: Additional secondary endpoints information will be collected for Bruising, Needle Bending/Breaking and Leakage in the Subject Diary.

For Needle Breaking, Bending or Injection Site Bleeding or Bruising, each subject will evaluate his/her perception of each by answering with a yes or no response.

For needle leakage, each subject will record leakage using the following scale (0-5):



3.2.3 Exploratory Endpoints

At the end of each study period, each subject will evaluate his or her perception of each of the following by answering with a yes or no response.

Teardrop Label Removal Force**:** The subject will be asked "Did you find the *teardrop label* easy to remove?" The response options will either be Yes or No.

Outer Cover Removal Force**:** The subject will be asked "Did you find the outer cover easy to remove?" The response options will either be Yes or No.

Inner Shield Removal Force: The subject will be asked "Did you find t the inner shield easy to remove?" The response options will either be Yes or No.

Ease of Insulin/Non-insulin Delivery: The subject will be asked "Were you able to deliver the insulin/non-insulin easily?" The response options will either be Yes or No.

3.2.4 Safety Endpoints

At 2nd and 3rd visits, presence and severity of any adverse events will be evaluated, recorded, and followed up as required.

For a complete list of survey questions, please refer to "Form: Questionnaire".

3.3 Acceptance Criteria

Primary Objective: Non-Inferiority Criterion (based on relative VAS where -75mm indicates a strong preference for Period 1 pen needle and +75mm indicates a strong preference for Period 2 pen needle) is -10mm.

Secondary Objectives:

For Overall Comfort, Anxiety Associated with a Needle Stick Injury, Injection Pain, and Ease of Use the Non-Inferiority Criterion is also -10mm.

For Needle Breaking, Needle Bending, Injection Site Bleeding, Bruising and Leakage Score > 1: The difference in occurrence rate with BD Nucleus pen needle vs Occurrence rate with Current pen needle will be compared to a 4% non-inferiority (NI) criteria.

Exploratory Objectives: No formal acceptance criteria has been established for this study.

3.4 Treatment Allocation and Methods to Reduce Bias

The order of the pen needle type (current vs. Nucleus) will be randomized for each subject. There will be no masking or blinding in this study.

3.5 Stopping Rules

No stopping rules for the study have been developed by the Sponsor. The Principal Investigator is responsible for suspending study enrollment for reasons of subject/clinician safety and well-being.

4.0 STUDY POPULATION

Approximately 260 subjects that are currently injecting, using a pen injector and pen needle:

- Insulin only
- Non-insulin injectable only (a minimum of once a day)
- Both-Insulin and a non-insulin injectable medication

A total of 240 evaluable subjects are needed to complete the study. A goal of 60 subjects per group (for 90% power) is targeted. Subjects may also be injecting other diabetes medications with a pen needle and pen device. If subjects use the same pen needle to inject both insulin and non-insulin medications, they will be asked to use the Nucleus product for both injections during the study. If subjects do not use the same pen needle to inject both insulin and non-insulin injectable medications, they will be asked to only use the medication (either insulin or non-insulin) with which they use one of the eligible pen needles.

4.1 Inclusion Criteria

Male and female patients will be considered for participation in the study if they fulfill the following conditions:

a. Adults (18 – 75 inclusive)

b. Diagnosed Type 1 or Type 2 diabetes

c. Every effort will be made to recruit approximately 25% Type 1 patients (of the total population, not of each subgroup) (minimum: 10%, maximum: 50%)

d. Every effort will be made to recruit a minimum of 30 subjects with Asian ethnicity (of the total population, not of each subgroup). Ideally, 60 Asian subjects are needed for the study.

e. Minimum within the last 4 months experience self-injecting insulin and/or non-insulin with a pen injector

f. Minimum within the last 2 months experience self-injecting consistently with one of the following available pen needles OR a subject may be enrolled that is using a 31G/32G pen needle that is not longer than 6mm in length who is willing to transfer to one of the following 32G pen needle with a 14 day wash-in period:
   i. Group 1: BD Nano 32Gx4mm
   ii. Group 2: NovoFine 32Gx6mm
   iii. Group 3: NovoTwist 32Gx5mm or
   iv. Group 3: NovoFine Plus 32Gx4mm
   v. Group 4: Owen Mumford PenTips 32Gx4mm or
   vi. Group 4: Perrigo / Ypsomed ClickFine 32Gx4mm or
   vii. Group 4: Other 32G such as UltiMed, MHC, or other private label.

g. Able and willing to provide informed consent/participant form

h. Able and willing to complete all study procedures

4.2 **Exclusion Criteria**

Subjects with any one of the following characteristics will be excluded from participation in this study:

a. Self-injecting with a pen injector for less than 3 months

b. Planned changes in diabetes medication regimen (increasing or decreasing number of injections per day).

c. Positive pregnancy test (self-attestation)

d. Currently taking anti-platelet therapy or anticoagulants (Use of up to 81 mg per day of aspirin is permitted).

e. History of a bleeding disorder or easy bruising

f. Blood borne infection(s)

g. History of recurrent dermatological conditions or skin disorder (e.g., psoriasis, eczema)

h. Gross skin anomalies and abnormalities (e.g., scars, stretch marks, discolorations, tattoos, superficial masses, acne, inflammation) located at or very close to the injection sites

i. Fear of needles, history of symptomatic low blood pressure or history of fainting (syncope) during hypodermic injections.

j. Use of any prescription analgesic medications within 24 hours of first study injection, and during the study.

k. A current or previous medical or physical condition that, in the opinion of the investigator, would place the patient at risk or make them unable to perform study procedures or has the potential to confound interpretation of the study results.

l. Currently participating in another study

m. Employed by, or currently serving as a contractor or consultant to BD or any diabetes injectable medication, insulin pen, or insulin pen needle manufacturer

5.0 DESCRIPTION OF STUDY PRODUCTS

5.1 Test Product(s)

- BD Nucleus pen needle – 4mm x 32G

5.2 Reference Products (Commercially Available Product)

- BD Nano 32Gx4mm
- NovoFine 32Gx6mm
- NovoTwist32Gx5mm
- NovoFine Plus 32Gx4mm
- Owen Mumford PenTips 32Gx4mm
- Perrigo / Ypsomed / ReliOn ClickFine 32Gx4mm
- Other 32Gx4, 5 or 6 mm: UltiMed, MHC, or other private label

5.3 Ancillary Products (if applicable)

Insulin/Non-insulin injectable pens that are compatible with reference pen needles.

5.4 Product Labeling

Investigational devices (or the immediate packaging) shall be labeled in accordance with regulatory requirements, including the following statement: "CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use." The unit label, at minimum on its immediate package must indicate “For Investigational Use only”, with full statement on the outer packaging.

For investigational products, box labeling will also include at a minimum:

- Product Identification
- Manufacture name and location
- EWO/Batch#
- Use by/expiration date
- Sterility Claim (sterile or non-sterile)
- “For Investigational Use only”

Commercial products will be supplied as labeled by the manufacturer.

5.5 Maintenance and Storage of Study Products

All pen needles should be stored according to the manufacturer's instructions. Refer to section 11.0 of the protocol for additional instructions regarding product disposition during and upon study completion (e.g., disposal, return or destruction, defective products).

6.0 STUDY METHODS

6.1 General Methods

This study will include up to 260 Type 1 and Type 2 diabetic subjects with Type 1 comprising of 24-130 subjects to the tested population. An effort will be made to recruit a minimum of 30 Asian descent to be included in the tested population. All subjects must be currently using an insulin/non-insulin injectable pen. No data will be collected from subjects/specimens after the point of discontinuation except as needed to follow ongoing adverse events. All study data collected from the subject up to the point of discontinuation will be recorded on the Case Report Form, entered into the study database, and included in subsequent analyses, as appropriate.

Subjects may be using medication pens for non-insulin injections such as GLP-1 agonists. Subjects may use both of these pens in the study, provided they use the same eligible pen needle for both injections. In the study, subjects will use the commercially available pen needle for 15 days and the Nucleus pen needle for 15 days, with the crossover period order depending on the randomization schedule. As the study progresses, restrictions may be placed on number of injections/day.

6.2 Visit 1: Screening and Enrollment

Prior to screening subjects for eligibility for the study, the PI or designee must obtain written informed consent from all potential subjects. Once consented, subjects will be assigned a subject number.
The following will be conducted by Site Staff to determine eligibility and to collect background/demographical information:

6.2.1 **Demographics/Diabetes History**: Subjects will be asked a number of background and demographic questions to ensure they meet the study-specific eligibility criteria. The PI or Investigator will review the medical history information self-reported by the subject; this information will be recorded in the source documents. Information collected will include, but is not limited to age, gender and diabetes history (Type 1 or Type 2, medications including dose and methods of delivery).

6.2.2 **Proficiency:** Subjects will be asked to perform a mock injection into an injection pad using a BD Nano pen needle. This will demonstrate their proficiency in injecting with a pen needle and pen device. If the subject is unable to demonstrated proficiency, s/he is discontinued from the study. The study staff will use a checklist to qualify the subject.

6.2.3 **Randomization: After each subject has completed the proficiency test, the subject will be** assigned a randomization number based on their pen needle group (Group 1-4), which will determine the order of the pen needed used in Period 1 or Period 2.

6.2.4 **Visit 1**

Non Wash-in Users

- Subjects will be randomized to Nucleus pen needle for the first 15-day period, then assigned commercial 32G pen needle for the second 15-day period OR assigned to commercial 32G pen needle for the first 15-day period, then the Nucleus pen needle for the second 15-day period (See randomization schedule).
- Subject will be instructed to use only the assigned pen needle during Period 1. If the subject is assigned to the Nucleus pen needle, they will be provided enough of the assigned pen needles until their scheduled return visit of 15-days. If the subject is assigned to the commercial 32G pen needle, they will use their current pen needle until the scheduled return visit of 15 days.
- Subject will be given a Diary 1 log to report events and answer questions during Period 1. Subjects will be trained on diary documentation.

Wash-in Users

- Subjects will be assigned a wash-in randomization number to determine their pen needle group (Group 1-4).
- Subjects will be instructed to use only the assigned pen needle during the Wash-in Period.
- Subjects will be provided enough of the assigned pen needles for Wash-in Period until their scheduled return for Wash-in visit in 14 days +/- 2.

6.3 **Wash-in Visit (Wash-in users only, See Section 3.1 for Wash-in Eligibility Criteria)**

- Wash-in Visit (14 days +/- 2 days from Visit 1)
- Subjects will be randomized to Nucleus pen needle for the first 15-day period, then assigned to commercial 32G pen needle for the second 15-day period OR assigned to commercial 32G pen needle for the first 15-day period, then the Nucleus pen needle for the second 15-day period (See randomization schedule).
- Subject will be instructed to use only the assigned pen needle during Period 1. Subjects will be provided enough of the assigned pen needles, regardless of whether they are randomized to Nucleus first or commercial 32G pen needle first, until their scheduled return visit of 15-days.
- Subject will be given a Diary 1 log to report events and answer questions during Period 1. Subjects will be trained on diary documentation.

6.4 **Visit 2 and 3**

Non Wash-in Users: Visit 2 (15 days+/- 3 days from Visit 1, no fewer than 13 days and no more than 17 days):

Wash-in Users: Visit 2 (15 days+/- 3 days from Wash-in visit, no fewer than 13 days and no more than 17 days):

- Diary will be collected and checked for completeness, and any clarifying questions will be asked. Study staff will review with subject all AEs, if applicable.
- Subject (Non-comparative) questionnaire will be completed by subject evaluating experience with assigned pen needle for Period 1.
- Subject will be instructed to use only the assigned pen needle during Period 2. If the subject is assigned to the Nucleus pen needle, they will be provided enough of the assigned pen needles until their scheduled return visit of 15-days. If the subject is assigned to their current pen needle,

they will use their current pen needle until the scheduled return visit of 15 days. If the subject is an individual who washed-in and is assigned to a new commercially available 32G pen needle, they will be provided enough of the assigned pen needles until the scheduled return visit of 15 days.

- Subject will be given a Diary 2 log to report events and answer questions during Period 2.

Visit 3 (15 days +/- 3 days from Visit 2, no fewer than 13 days and no more than 17 days)

- Diary will be collected and checked for completeness, and any clarifying questions will be asked by PI or designee. Study staff will review with subject all AEs, if applicable.
- A non-comparative questionnaire will be completed by each subject evaluating experience with assigned pen needle for Period 2.
- A comparative questionnaire will be administered comparing the pen needles from the two periods.

7.0 INTERRUPTION OR DISCONTINUATION OF PARTICIPATION/TESTING

7.1 Discontinuation of Study Subjects

Subjects may request withdrawal from the study at any time or may be withdrawn at the discretion of the Principal Investigator for any of the following reasons:

- Adverse Event/Concurrent Illness
- Noncompliance with study requirements or restrictions
- Failure to meet ongoing inclusion criteria, or development of an excluding condition
- Protocol deviation
- Withdrawal of consent
- Subject is lost to follow up
- Administrative issues
- Any other reason which, in the opinion of the PI, makes the subject's participation in the study not in his or her best interest.

7.2 Discontinuation Visits and Follow-up Procedures

For subjects discontinued due to adverse events, the clinical course of the event will be followed according to accepted standards of medical practice until the event resolves, stabilizes, or in the opinion of the Investigator, is no longer considered clinically significant.

8.0 RISK / BENEFIT ASSESSMENT

8.1 Potential Risks

The risks to the subject are non-significant and the findings may reveal information that may improve medical care for persons with diabetes. The potential benefit to medical practice outweighs the non-significant differential risk compared with current standard of care, experienced by the study subject. As a result of inserting a pen needle, subjects may experience pain, bleeding, or local infection. However, given the size of the investigational pen needles (4mm x 32G) and the procedures being used in disinfecting the skin prior to inserting the pen needle these risks are negligible.

Risks associated with a pen needle injection may include:

- Discomfort or pain
- Fainting
- Bleeding
- Bruising
- Redness
- Infection

8.2 Potential Benefits

There are no direct benefits to the subject for participation in this study. The findings may reveal information that will allow for a better understanding of insulin/non-insulin pen needle, and thus may improve medical care for persons with diabetes.

9.0 SAFETY

9.1 Adverse Event Definitions

Adverse Event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease in a subject that is temporally associated with the use of an investigational product or procedures, even if the event is not considered to be related to the study product or procedures.

This includes events not seen at baseline and events that have worsened if present at baseline. The term AE will refer to all adverse events (serious and non-serious) occurring during participation in a study of either investigational devices and/or drugs.

Serious Adverse Event (SAE): An SAE is any AE occurring during study participation that results in any of the following outcomes:

- Death
- Life Threatening (refers to any event in which the subject 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)
- Hospitalization or prolongation of a hospital stay
- Persistent or significant disability or incapacitation (refers to any event which results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions)
- Required intervention to prevent permanent impairment/damage
- Congenital anomaly/birth defect
- Important medical event that may require intervention to prevent one of the preceding conditions.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Refer to Protocol Section 8.1 (Potential Risks) for a list of *anticipated* adverse events, signs or symptoms. (21CFR-812.3(s))

9.2 **Adverse Event (AE) Management**

At each study contact, subjects will be questioned in an open-ended manner regarding any new or worsening undesirable signs or symptoms they may have experienced since the previous contact. Elicited signs and symptoms must be comprehensively documented on the appropriate source documentation.

Each sign, symptom, disease or illness reported must be evaluated by the Investigator or designee to determine if it meets the definition of an Adverse Event.

The clinical course of the event will be followed according to accepted standards of medical practice until the event resolves, stabilizes, or in the opinion of the Investigator, is no longer considered clinically significant. The Investigator must supply the Sponsor with information concerning the follow up and/or resolution of the AE.

Some reported or observed signs and symptoms are inherent to subcutaneous injection and are likely to occur transiently for nearly all subjects in this study. Such signs or symptoms will not be considered AEs as long as they are mild (transient, easily tolerated, no interference with daily activities) and the Principal Investigator agrees. The following will not be not be considered AEs:

- Mild, self-limited pain, swelling at the injection site
- Mild bruising at the injection site
- Mild self-limited bleeding at the injection site

However, these signs and symptoms ***must be considered AEs and*** documented on the Adverse Event CRF should any of them occur in such a way that the extent or nature of the experience exceeds that normally associated with the procedure, as judged by the Subject to be excessive pain, bruising or bleeding.

All needle breaking ***must be considered AEs and*** documented on the Adverse Event CRF.

Some signs and symptoms are inherent to the conditions under study (i.e. diabetes) and are likely to occur transiently for nearly all subjects in this study. Episodes of hyperglycemia and hypoglycemia occurring after subject enrollment and exposure to study product and/or study procedures, should be reported based on the following criteria:

- All blood glucose values <50 mg/dL (hypoglycemia) or >400 mg/dL (hyperglycemia) that require 3rd party (defined as, assistance of another person to administer carbohydrates or glucagon) or medical assistance for recovery will be recorded as an AE and assessed for seriousness.
- Any self-identified hypoglycemia or hyperglycemia without a BG reading or with any BG reading that requires 3rd party or medical assistance for recovery will be recorded as an AE and assessed for seriousness.
- BG >400 mg/dL (and no symptoms of ketosis) will not be considered an AE.
    - Signs of ketosis are elevated BG along with nausea but individual has the ability to drink fluids and nausea is resolved with additional insulin and oral fluids, this may be considered an AE per the discretion of the PI or designee.

All blood glucose values <50 mg/dL, or self-identified as hypoglycemia that resolves with standard carbohydrate administration will not be recorded as an AE unless otherwise determined by the Principal Investigator. However, these signs and symptoms ***must be considered AEs and*** documented on the Adverse Event CRF should any of them occur in such a way that the extent or nature of the experience exceeds that normally associated with the procedure, as judged by the PI, or the event meets the criteria for a Serious Adverse Event (SAE).

9.3 **Assessment of Adverse Events (AEs)**

All AEs must be assessed for Seriousness, Severity, and Relationship. All AEs, regardless of classification, must be comprehensively documented in the CRF and on the SAE form, if applicable, and reported to BD. This includes AEs related to marketed study products. The following information about the event is to be reported on the AE CRF:

- Seriousness, classified as: Non-Serious or Serious
- Severity, classified as:
  - Mild: Transient symptoms, easily tolerated, no interference with daily activities
  - Moderate: Marked symptoms, moderate interference with daily activities, tolerable
  - Severe: Considerable interference with daily activities, intolerable
- Relationship, to the study product or study procedures:
  - Not Related: Evidence suggests absolutely no possible causal relationship between the event and the investigational study device (or procedures).
  - Unlikely Related: Evidence suggests that other possible causes or contributing etiological factors may have caused the event other than the investigational study device (or procedures).
  - Possibly Related: Evidence suggests a causal relationship between the event and the investigational study device (or procedures) cannot be ruled out
  - Related: Evidence suggests a reasonable causal relationship between the event and the device (or procedures) is likely

In addition, the following should be recorded for each AE:

- Action(s) taken to remedy the AE, including change in study treatment or participation, or medical/surgical treatments
- Duration of the AE from onset through resolution, as applicable
- Cause (including suspected product/procedure and/or other cause)
- Outcome of the event, including resolution and sequelae, as applicable

9.4 **Additional Procedures for Assessing & Reporting Serious Adverse Events (SAE)**

SAE criteria are specified in Section 9.1. All SAEs must also be assessed by the Investigator and Sponsor Medical Monitor to determine whether an SAE is expected or unexpected. An adverse event will be considered unexpected or unanticipated if the nature, severity or frequency of the event is not consistent with the risk information previously described in the protocol, Informed Consent, or Investigator's Brochure (if applicable).

Any adverse event meeting the criteria for 'Serious', regardless of the Investigator's opinion of expectedness or relationship to the study product, must be reported to BD within 24 hours. The Investigator or designee must report the event by telephone or email to the Study Monitor. In addition to reporting the SAE to the Study Monitor, the Investigator must also submit a completed SAE form to the BD Trial Safety Dept. via fax or email listed below within 24 hours of receipt of the information.

- Safety Fax Line: (US) 1-201-847-5688
- Safety Email: BD_Trial_Safety@BD.com

Medical questions about study safety issues and serious adverse events can be directed to the Sponsor Medical Monitor.

9.4.1 Reporting Obligations to IRB/EC and Health Authorities

The Investigator must report any adverse events which are serious, unanticipated/unexpected and probably or possibly related to the study product or procedures to the reviewing IRB/EC. This report must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event.

The Investigator may also have additional responsibilities for AE reporting to their governing Health Authority which they are responsible for identifying and fulfilling.

The Sponsor will provide results of any evaluation of an unanticipated/unexpected adverse device effect to appropriate Health Authorities, to all Investigators, and to all reviewing IRB/ECs within 10 working days after the Sponsor is notified of the event. If the Investigator wishes to assume responsibility for filing reports of evaluation results to their own IRB/EC in lieu of the Sponsor, they must notify the Sponsor in writing of this preference and must retain evidence of their compliance with this requirement.

BD will comply with all other Sponsor safety reporting requirements and timelines for other entities (e.g., Data Safety Monitoring Boards) and local health authorities in other countries where this study or other studies with the same product are being conducted, in compliance with study procedures and applicable local regulatory requirements and BD Standard Operating Procedures.

10.0 INCIDENTS

A Clinical Study Incident is defined as any problem or issue involving the investigational product(s), reference methods, associated procedures or equipment, or represents a product-related injury (or potential for injury) to study subjects or personnel as a result of execution of this protocol. Clinical Study Incidents may adversely (or potentially adversely) affect human safety, the integrity of the evaluation data, or the operation of devices or systems, and warrant prompt attention.

Incidents involving injury to study subjects will also be reported as Adverse Events (refer to Section 9). Examples of Clinical Study Incidents that are not Adverse Events might be **mislabeling or adulteration of the investigational device, equipment or device malfunctions, errors in the device instructions, damage to devices caused by shipping or handling or improper storage, or injury to study personnel due to execution of the protocol**. If appropriate, an Incident may also be documented and reported as a protocol deviation.

Study-specific procedures for reporting Incidents, as well as adverse events and protocol deviations, will be provided to the study site prior to study execution. The Monitor should be contacted immediately when site becomes aware of or suspects any defective or malfunctioning product. This includes:

- Products that are involved in Study Incidents,
- Products that are found to be expired, damaged or defective,
- Products that are possibly the cause of an adverse effect, regardless of whether the product was believed to be damaged, defective or malfunctioning.

Such products (whether investigational or marketed) should be segregated and returned with appropriate documentation to the BD address below, unless instructed otherwise by BD. The Study Monitor should be contacted with any questions regarding return of study products. BD will supply mailing kits specifically intended for product contaminated with potentially bio-hazardous material.

11.0 RETURN OR DESTRUCTION OF STUDY PRODUCT

All disposable, used products not failed, damaged or otherwise involved in an Incident or Adverse Event are to be discarded into appropriate waste containers at the investigational site.

Unless instructed otherwise by BD, the Investigator will return all remaining unused or unopened test, reference, and ancillary study products to BD. At the conclusion of the study, and as appropriate during the course of the study, any products, supplies or BD equipment that are required to be returned will be shipped to BD at the address below, unless instructed otherwise:

Falguni Patel
Becton, Dickinson and Company
1 Becton Drive, MC 250
Franklin Lakes, NJ 07417
201-847-4688

11.1 Defective or Failed Study Products

DFSP: The term DFSP generally refers to any damaged, malfunctioning, or failed product (confirmed or suspected) identified at the investigational site. DFSP includes:

- Products that are involved in Study Incidents,
- Products that are found to be damaged or defective,
- Products that fail or malfunction during the study,
- Study products rendered unusable due to subject/patient/site staff mis-use or improper storage conditions,
- Products that are possibly the cause of an adverse effect, regardless of whether the product was believed to be damaged, defective or malfunctioning.

The Monitor must be contacted immediately when site becomes aware of any DFSP. All DFSP (whether investigational or marketed) should be segregated and returned with appropriate documentation to the BD address above, unless instructed otherwise by BD. The Study Monitor should be contacted with any questions regarding return of study products. BD will supply mailing kits specifically intended for product contaminated with potentially bio-hazardous material.

Depending on the intended use of the study products in the study (e.g., if assessing failure modes), there may be exceptions or additions to the requirements for DFSP/Incident documentation; these will be described in this protocol or the study-specific Monitoring Plan.

12.0 DATA COLLECTION AND MANAGEMENT

12.1 Source Documents

Source data includes all information in original records (and certified copies of original records) of clinical findings, observations, or other activities (in a clinical study) used for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies) and are used to verify the authenticity of information recorded on the Case Report Form (CRF). Typical source documents include the hospital chart, medical office file, laboratory report, clinician notes, patient record, recorded data from automated instruments or other documentation prepared and maintained by the investigator/staff or ancillary services which contains a record of all observations and other data pertinent to the investigation on a study subject.

The investigator is required to maintain original source documents at the site. Should an original source document (e.g., an instrument printout, direct entry CRF) need to be forwarded to BD for data entry, the site must retain a clearly designated certified copy. The Study Monitor will confirm that procedures for copy certification have been established at the site prior to transmittal of any original source documents.

12.2 Case Report Forms (CRF)

The case report forms (CRF) will be provided by the Sponsor. The term "CRF" as used in this protocol may refer to traditional paper CRFs, or electronic case report forms for electronic data capture (EDC), as determined by the Sponsor.

The Investigator may delegate CRF completion to study personnel. However, the Sponsor must be apprised in writing of the name of such persons and the scope of their authority. The Principal Investigator or designee is obligated to review each CRF page and sign or initial the indicated pages using ink or for EDC, an electronic signature. An individual record will be kept for each subject that provided informed consent.

All entries to a paper CRF should be made clearly in black or dark blue indelible ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections are made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

CRF entries will be compared to source documents by the study monitor or designated personnel. Unless specified otherwise, all information on the CRFs must be traceable to original source documents.

12.2.1 CRF as Source Document

In this study, the following CRFs will serve as original source documents: Visual Analog Scale for preference, component preference, overall comfort, anxiety, pain, bruising, bending and ease of use. A questionnaire will be used for exploratory outcomes.

- Demographics/Diabetes History
- Diary:
  - Injection Log (Leakage, Bruising, Bleeding, Needle Bending, Needle Breaking)
  - AEs
  - Product Issues
- Subject (Non-comparative) Questionnaire
- Comparative Questionnaire

12.2.2 CRF/Data Transmittal

Instructions for CRF Transmittal will be provided to the site at Study Initiation. Specific procedures may be described in a study-specific Monitoring Plan.

Instructions for CRF Transmittal will be provided to the Investigator at Study Initiation. Specific procedures may be described in a study-specific Monitoring Plan.

12.3 Data Management and Storage

Data Management will be performed by the Sponsor. Data from completed CRFs will be entered into a controlled database and the database verified for accuracy against the CRFs, when applicable. If electronic data capture is utilized, the electronic records entered at the site will be entered directly into the controlled database. Data security is ensured through password protection, limited access, audit trails, and regular backups of the data. Upon completion of the study and verification of data, data will be screened for accuracy and completeness, after which the database will be locked from any additional changes. A copy of the locked database will be provided to the BD Corporate Statistics Department for statistical analysis.

13.0 STATISTICAL METHODS

Statistical methods will be detailed in a Statistical Analysis Plan. Any deviations from the original statistical plan will be justified and described in an amended statistical analysis plan and/or the protocol, or the final statistical and study report.

13.1 Sample Size Determination

Based on previous studies, SD for relative VAS is assumed to be ~35mm. A sample size of 60 subjects has 90% power of passing a 10mm NI criteria, assuming a true average of 5mm in favor of Nucleus (2-sided 95% CI for the mean). A sample size of 45 subjects is sufficient to provide 80% power. These sample size apply to each subgroup for which a NI (or superiority) claim is desired.

13.2 Data Evaluability

All data collected will be analyzed, subject to review for possible exclusion based on significant protocol deviations (e.g. failure to follow randomization scheme).

13.3 Statistical Methods

All analyses will be performed and presented per subgroup (Group 1 – Group 4) first (with no alpha adjustment). For each response, a statistical test will be applied to determine whether it is valid to combine the results from the four study group into one overall result. If significant differences between the groups are identified, combined results will only include results from the groups exhibiting no significant difference; groups that are significantly different (if any) will not be grouped into the overall result.

If a sufficient number of subjects having a two-weeks wash-in period, are enrolled in the study, a comparison of the responses may be performed. The comparison will be conducted between the subjects who did wash-in and those who did not wash-in for all groups pooled together.

Descriptive statistics (number of observations, mean, standard deviation, minimum, maximum and 95% mean confidence interval) will be calculated and presented for all quantitative responses. Frequency tables with number of observations, percentage of total and 95% confidence interval (score method) for the percentage (as applicable) will be created for discrete responses.

Analysis for relative VAS: For each outcome measured on a relative VAS, a two-sided 95% confidence intervals will be calculated for the average rating. A modeling approach may be used to adjust for the visit effect (because of the often observed bias towards favoring the last PN used). Results will be tested for non-inferiority, followed by superiority:

If the lower bound of the CI is > -10mm, we can conclude in non-inferiority

If the lower bound of the CI is > 0mm, we can conclude in superiority

Analysis for needle breaking, needle bending, injection site bleeding, and bruising: A 95% confidence interval for the following difference in two independent proportions will be calculated using the score method:

Proportion with BD Nucleus PN – Proportion with Current PN

The upper bound of the confidence interval will be compared to the 4% NI criterion: non-inferiority will be concluded given the upper bound of the 95% score interval for the difference in proportions is < 4%.

Analysis for needle leakage: Distribution of leakage scores will be provided and proportion of injections with recorded leakage score > 1 will be calculated per pen needles in each subgroup. Same analysis as for needle breaking, needle bending, injection site bleeding or bruising will be performed using proportion of injections with recorded leakage score > 1 as the response.
Exploratory endpoints will be summarized with proportion of "Yes" answers and 95% score confidence interval.

13.4 Demographics/Other descriptive information

Demographic variables will be summarized for all subjects in each study group. Count, mean, standard deviation, median, min, and max values will be calculated for the continuous variables. Count and percentage will be calculated for the categorical variables.

Subject disposition will be tabulated.

13.5 Safety Analysis

Data listings will be provided for any adverse event and serious adverse event. Adverse events will be summarized descriptively by pen needle and study subgroup.

13.6 Interim analysis

None planned.

13.7 Additional analyses

None planned.

14.0 QUALITY CONTROL AND ASSURANCE

14.1 Accountability of Study Products

Investigational study products will be released only for use by Investigators who have obtained written IRB/EC approval (as required) for participation in this study, who have completed all required study documentation, and who have been qualified by the Sponsor. Investigators must maintain control over all

study products, and ensure they are used in accordance with this protocol. Failure to do so may result in the Sponsor suspending or terminating the study at the Investigator's site.

The Investigator will ensure that study products are only dispensed to subjects (or used for specimens) properly enrolled in the study. The Investigator must maintain records of receipt, disposition, return and/or destruction of all study products. All investigational study products released to the site must be accounted for at the unit level prior to study close out, regardless of disposition. The Study Monitor will regularly review all records regarding study product accountability.

The Sponsor will maintain records that document the shipment, receipt, disposition, return and/or destruction of study products.

14.2 Monitoring

BD, the study sponsor, will designate trained and qualified personnel to monitor the progress of this clinical study in accordance with BD Monitoring SOPs and the study-specific Monitoring Plan. A pre-study site qualification visit will be conducted to assess the adequacy of the site facilities and staff with respect to study requirements.

Prior to study start, a study initiation visit will be conducted to provide training to site staff with regard to the protocol, the completion of study documentation and Case Report Forms (CRFs), the monitoring schedule, and all regulatory requirements. During the study, routine monitoring visits will be conducted to assure the site continues to adhere to the protocol, the investigator agreement, and regulations regarding conduct of clinical studies. Assessments will be made regarding the subjects' protection and safety, when relevant, as well as the quality, completeness, and integrity of the data. The Study Monitor will assist the investigative site with query resolution and will perform site close-out activities once all queries have been resolved.

Additional visits may be carried out depending upon site activity and performance. The Investigator must agree to the inspection of all study related records and give direct access to source documents for verification of data on CRFs.

The Investigator is responsible for ensuring that any site-owned equipment required for use in the study is properly installed and maintained (e.g., inspected, calibrated, alarmed). Documentation of equipment maintenance procedures must be available for review by the Monitor.

14.3 Audits and Inspections

If the study is selected for audit by the Sponsor or if there is an inspection by the appropriate Health Authorities, then the Investigator and his team will make themselves available during the visit. The Investigator must agree to the inspection of all study related records and give the auditor/inspector direct access to source documents for verification of data on CRFs. The subject's anonymity must be safeguarded and data checked during the audit remain confidential.

As soon as the Investigator is aware of an upcoming inspection/audit by the Health Authorities, he/she will promptly inform BD. As agreed with the Investigator, BD personnel may be present at the site during the inspection.

14.4 Protocol Deviations

Protocol deviations are not permitted and should be implemented prospectively as a protocol amendment whenever practical or appropriate, unless required to protect the safety and well-being of the subject. The Investigator must notify the Sponsor immediately of any such deviation resulting from the need to protect a subject.

Protocol deviations (other than those required to protect the safety and well-being of a subject) may impact the evaluability of study data, and may place subjects at risk. If the Investigator or their staff inadvertently deviates from the study plan, the Investigator should implement appropriate corrective and preventive procedures, and should notify the Sponsor at their earliest convenience. Significant deviations may also need to be reported to the IRB/EC and local health authority.

The Study Monitor will evaluate records of study conduct at the site to identify any deviations, and will also report them to the Sponsor. Upon evaluation by the Sponsor, actions may be required to prevent additional deviations, such as retraining of the site, implementation of additional site procedures, and more frequent monitoring. If these steps fail, more serious measures, up to and including termination of the site and withdrawal of study product may be necessary.

15.0 ETHICAL AND REGULATORY STANDARDS

15.1 IRB/EC

An appropriate IRB/EC must review this protocol, the Informed Consent Form (if applicable), and any other supporting study documents which affect subject or study personnel safety, prior to study initiation at an investigational site. No investigational site may begin the study until the IRB/EC has given its written approval, signed by the IRB/EC chairperson or authorized personnel, and a copy of the approval letter and the approved Informed Consent Form (if applicable) has been provided to the Sponsor.

15.2 Informed Consent

Prior to giving informed consent, each candidate will have the opportunity to review the study procedures, risks and benefits and ask any questions he or she may have regarding the study. Before enrolment, each subject must give informed consent, documented by signing a written form, created and approved in compliance with 21 CFR Part 50.25 and 21 CFR Part 56. Each subject should be given a copy of the signed informed consent document.

15.3 Confidentiality of Data

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and BD and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. Subject confidentiality and anonymity will be maintained at all times by removal of all identifiers from any data, clinical samples or documentation submitted for this study.

Any data collected meeting the definition of PHI will be collected and maintained using the designated authorizations and following all privacy procedures as specified in the applicable health authority regulations.

BD will maintain the security and confidentiality of all clinical study data sent to BD. BD clinical study databases will not be shared with any third party without the express written consent of the Principal Investigator and/or Site.

The Study Monitor or other authorized representatives of BD may inspect all documents and records required to be maintained by the Investigator. The Site will permit access to such records. BD and the Site may be required to provide regulatory agencies access to clinical study data and records, as well as source documents.

All other agreements as to confidentiality by BD, the Principal Investigator, and the Site may be found in the Confidential Disclosure Agreement and the Clinical Trial Agreement.

15.4 Protocol Modifications

Amendments to the protocol will not be implemented without agreement from the Sponsor and prior submission to and written approval from the governing IRB/EC, except when necessary to eliminate an immediate hazard to the subject. Notice of an emergency modification shall be given to the Sponsor and the reviewing IRB/EC as soon as possible, but in no event later than 5 working days after the emergency occurred. Protocol amendments may affect Informed Consent Forms for current and future subjects.

Minor changes to the protocol, such as correction of typographical errors or changes in personnel names (other than the PI) or contact information will be processed as administrative changes. Administrative changes will be submitted to the governing IRB/EC but implementation of the administrative change may proceed without prior IRB/EC approval, unless so required by the IRB/EC or site SOPs.

15.5 Study Discontinuation

BD reserves the right to temporarily suspend or prematurely discontinue the study at a single site or at all sites at any time and for any reason. If such action is taken, BD will discuss the reasons with all Investigators (the Investigator). If the study is terminated or suspended due to safety reasons, the sponsor will inform the health authorities as required, and provide the reason(s) for the action. Investigator(s) must inform their IRB/EC promptly and provide the reason(s) for the suspension or termination.

15.6 Clinical Study Registration

In compliance with Title VIII of Public Law 110-85, known as FDA Amendments Act of 2007 (FDAAA), BD will register all applicable studies and disclose study results in a publicly accessible database, e.g. the ClinicalTrials.gov web site. Applicable studies will be registered no later than 21 days after commencing enrollment. Study results for applicable studies will be posted to the website within 12 months of the last subject visit for collection of primary outcome data, or after health authority approval for previously unapproved devices. BD has responsibility for determining whether this study qualifies as an "applicable" study under the law, and if so, will take responsibility for registration and disclosure as required by law.

15.7 Publication of Results

BD believes that results of applicable clinical studies of our products should be published in peer-reviewed literature in a timely, accurate, complete and balanced manner, regardless of study outcomes. BD is committed to making information public whenever it relates to the safety and efficacy of its marketed products.

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the investigator(s) and the appropriate personnel of BD. Authorship will be based on generally accepted criteria of the ICMJE (International Committee of Medical Journal Editors) and determined by mutual agreement. For multi-center studies, the first publication will be based on data from all centers, analyzed as stipulated in the protocol by BD statisticians, and not based on data from single sites or a subset of sites. Investigators participating in multi-center studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other investigators and BD (the sole exception being an unanticipated adverse event that is product-related and which might have clinically significant safety implications for a marketed product or a class of products).

BD must receive copies of any intended communication in advance of publication as specified in the Clinical Trial Agreement. In a timely manner, BD will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and to provide any relevant supplementary information to the investigators.

15.8 Record Retention

If the Principal Investigator or Clinical Center withdraws from the responsibility of keeping the study records, custody must be transferred to a person or entity who will accept the responsibility. BD must be notified in writing of the name and address of the new custodian.

Federal regulations require that a copy of all essential study documents (e.g., IRB/EC approvals, signed informed consent forms, source documents, CRF copies, safety reports, test article dispensing records, etc.), must be retained in the files of the responsible Investigator for a minimum of 2 years following notification by BD that all investigations are completed, terminated, or discontinued, or that the FDA has approved the application (21 CFR 812.140).

16.0 BIBLIOGRAPHY/REFERENCES

None

17.0 PROTOCOL REVISION HISTORY

Version #	Rationale for Change	Section or Page affected	Description of change
1.0	New Protocol		
2.0	Allow for visit 2 and 3 timing flexibility, no effect on data collection	*Section 3.1 and 6.3*	(up to 3 days after study period is completed)
2.1	Typo	*Cover Page*	Correct date for Version History for Version 1.0 August 16, 2017 to Version 1.0 August 7, 2017
2.2	Typo	*Header*	Corrected header and updated to Version 2.2 and corrected date
3.0	Update for visit 2 and 3 timing flexibility, no effect on data collection	*Section 3.1 and 6.3*	+/- 3 days, no fewer than 13 days and no more than 17 days
4.0	Non-insulin users use these 32G pen needles for non-insulin injections. Addition of 31G user with wash-in, to increase subject pool.	*Section 1.0, 2.0. 3.0, 3.2.3, 4.0, 4.2, 4.3, 5.3, 6.0, 8.2*	Added that non-insulin users only using pen needles for non-insulin injections could also be included in the study. The users needed a minimum of one injection of non-insulin per day. Added 31G users with a wash in who were willing to switch to a 32G for the period of the study.

Version #	Rationale for Change	Section or Page affected	Description of change
4.1	Formatting corrections	*All*	Formatting of Heading 2 was corrected.
5.0	Broadened groups to allow wash-in of 32G x 4mm/5mm/6mm user to increase subject pool Inclusion/Exclusion Criteria	*Section 3.1* *Section 4.0*	Subjects using 32G under 6mm in length (such as BD Nano) could be washed-in to fill up other groups Decrease in I/E Criteria from 6 months to 3 months for self- injecting with a pen injector and decrease from 3 months to 1 month for use with one of the competitor products

18.0 APPENDICES

The following appendices are attached:

18.1 Non-comparative Questionnaire

18.2 Comparative Questionnaire

18.3 Diary

18.4 Randomization Schedule

18.5 Proficiency Questionaire

Signature Page for DBC-17NUCLS07 Protocol

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