Statistical Analysis Plan

Protocol Number/version	DBC-18PENDL02/Version 4.0 25Feb2019
Protocol Title	Comparative User Experiences with BD Nano™ PRO 4mm × 32G Extra Thin Wall Pen Needle vs the Artsana Insupen® Extr3me 4mm × 33G, Artsana Insupen® Extr3me 3.5mm × 34G and the Simple Diagnostics Comfort EZ™ 4mm × 33G Pen Needles
SAP Date	May 30, 2019
Version History	March 5, 2019: Original Release May 14, 2019: Additional analysis for site effect was added in Section 6.2.1 to 6.2.4. Potential DBC-18PENDL01 and DBC-18PENDL02 combined analysis was added in Section 6.2.1.1, 6.2.2.1, 6.2.3.1 and 6.2.4.

Approval

Signature below indicates approval of the statistical analysis plan as written.		
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Contents

1 List of Abbreviations and Definitions

- **AE:** Adverse event
- **BD:** Becton Dickinson and Company
- **GCD:** Global Clinical Development, BD
- **CI:** Confidence Interval
- **CRF:** Case Report/Record Form
- **G:** Gauge
- **IFU:** Instruction for Use
- **NI:** Non Inferiority
- **VAS:** Visual Analog Scale
- **RS:** Randomization schedule
- **SAE:** Serious Adverse Event
- **SAP:** Statistical Analysis Plan
- **SD:** Standard Deviation

2 Overall Study Description

2.1 Study Background

Pen needles are a component of pen-based injection systems routinely utilized for parenteral administration of medications such as insulin. In 2010, BD introduced a 4mm × 32G pen needle. At that time it was the shortest and thinnest pen needle available. In addition to lowering the risk for intramuscular injections, this pen needle was demonstrated to be preferred by patients vs. their current pen needles. Since its introduction, competitors have launched similar length pen needles with thinner gauge needles, such as 33G and 34G. The intent of this comparative use study is to determine whether patient experiences are different when using the BD Nano™ PRO 4mm × 32G extra thin wall, 5-bevel pen needle (herein referred to as BD Nano™ PRO) vs competitive thinner pen needles - Artsana Insupen® Extr3me 4mm × 33G, Artsana Insupen® Extr3me 3.5mm × 34G and the Simple Diagnostics Comfort EZ™ 4mm × 33G Pen Needles (herein referred to as comparators). These experiences include injection pain, force to deliver dose, bending, and ability to deliver full dose (leakage).

2.2 Study Objectives

- **Primary Objective**
  Demonstrate non-inferiority of the BD Nano™ PRO pen needle compared to each of three (3) commercially available comparators (33G and 34G) for injection pain.

- **Secondary Objectives**
  Demonstrate superiority of BD Nano™ PRO vs each of 3 comparator pen needles for the following:
  1. Leakage from the needle tip and the injection site (measurements combined) after removal from body
  2. Subject perceived force required to deliver dose
  3. Patient end needle bending after removal from body
  4. If primary outcome demonstrates non-inferiority then evaluate for superiority of BD Nano™ PRO vs each comparator.

- **Exploratory Objectives**
  Compare BD Nano™ PRO vs each of 3 comparator pen needles for the following:
  1. Injection time
  2. Patient end needle breaking at any time
  3. Survey responses pertaining to subjective assessments of pen needle characteristics

2.3 Study Design

This is a subject partially blinded, block randomized, prospective, single-visit, multi-center study to compare user experiences with BD Nano™ PRO pen needle vs. three (3) thinner commercially available comparator pen needles (Artsana Insupen® Extr3me 33G, Artsana Insupen® Extr3me 34G and the Simple Diagnostics Comfort EZ™ 33G Pen Needles). The study will include up to 146 study subjects having Type 1 or Type 2 diabetes. Study conduct will consist of one 60 to 120 minute site visit in which pre-set doses of saline will be abdominally delivered by subjects via a reusable insulin pen device. All pen needles will be attached by study staff and pen needle outer cover and inner shield will be removed for subjects. Subjects are to perform 12 injections into the abdomen (6 pairs of injections). Pairs of injections will be evaluated and each pair will contain one BD Nano™ PRO and one comparator pen needle. Within the 12 injections, each comparator will be injected twice, therefore each subject will experience 2 of each of the following pairs:

- BD Nano™ PRO pen needle vs Artsana Insupen® Extr3me 4mm × 33G × 2
- BD Nano™ PRO pen needle vs Artsana Insupen® Extr3me 3.5mm × 34G × 2
- BD Nano™ PRO pen needle vs Simple Diagnostics Comfort EZ™ 4mm × 33G × 2

Subjects will not see pen needle labels or be informed which pen needle is being used to inject. The BD Nano™ PRO has a distinct configuration and subjects will most likely notice the difference vs the comparators. Subjects will not be informed of the BD's or the comparator's pen needle brand, length or gauge. The pen needle order within the pairs of injections will be randomized for each subject and the pairs will be randomized to various abdominal injection sites within each subject. Besides being informed of the requirement to insert the pen needles "straight-in" (perpendicular), subjects will be instructed to use their usual injection technique.

2.4 Endpoints

2.4.1 Primary Endpoints

Injection Pain: Each Subject will evaluate pain after completion of each pair of injections using a 15 cm relative Visual Analog Scale (VAS).

2.4.2 Secondary Endpoints

After each injection:

- **Leakage**: After saline delivery equivalent to 30U of U100 insulin (0.3mL) and subject removal of pen needle from body, study staff will use the provided materials and scale to absorb leakage from the pen needle tip and injection site to measure the amount of leakage.
  Leakage will be considered to be present if measurement is equivalent to or greater than 5% of dose (equivalent to $\geq 0.015g$).

- **Needle bending**: Study staff will use a provided needle bend scale and visually inspect retained pen needles to determine the presence of bending. If present, study staff will determine and document degree of bend with the provided scale. For the purpose of answering the study objective, needle bend will be considered if the bend rating ≥ 2.

After each pair of injections:

- **Injection force**: Each subject will evaluate perceived injection force after each pair of injections using a 5-point Likert scale (from 1st injection required much less force to deliver medication to 2nd injection required much less force to deliver medication).

2.4.3 Exploratory Endpoints

During each injection: Injection time - includes the following time periods for each injection

- Time from when subject first pushes injection button to time button fully depressed (delivery time)
- Time from when injection button fully depressed to when pen needle removed from body
- Total injection time - the 2 time periods above combined

After each injection:

- Breaking: Study Staff will record any patient end needle breakage. Breakage is defined as the patient-end metal cannula separated into two pieces.

After all injections completed:

- Survey responses: Subject completes a 5-point Likert scale survey (from Disagree to Agree). Subject will be instructed to respond to the questions based on their usual (in-home use) injection experience. Subject responses to survey questions will be tallied. The survey includes the following four questions:

  1. Injection pain affects my level of satisfaction with my treatment.
  2. Injection pressure needed to deliver the dose affects my level of satisfaction with my treatment.
  3. Post injection leakage increases my level of concern that I may not be receiving my full dose of medication.
  4. A bent needle increases my level of concern about the reliability of my injection.

2.4.4 Safety Endpoints

Occurrence of adverse events will be evaluated, recorded, and followed up as required.

2.5 Acceptance Criteria

2.5.1 Primary Objective

BD Nano™ PRO non-inferior to each comparator for injection pain with partially blinded injections based on relative VAS, where -75mm indicates worse pain for BD Nano™ PRO and +75mm indicates worse pain for comparator with a non-inferiority criterion of -10mm.

2.5.2 Secondary Objectives

- The BD Nano™ PRO will be evaluated for superiority vs each comparator for leakage, injection force, and bending.

- If the BD Nano™ PRO demonstrates non-inferiority for injection pain for the Primary Objective, compare the BD Nano™ PRO vs each comparator for superiority.

2.5.3 Exploratory Objectives

No formal acceptance criterion has been established for the following objectives - time to deliver dose, total injection time, and survey responses after all injections completed.

3 Sample Size

Pain: Assuming the SD for relative VAS is around 50mm (based on DBC-17NUCLS07), a sample size of 266 pairs per each comparator has >90% power of passing a -10mm NI criteria, assuming no true difference in pain (based on a 2-sided 95% CI for the mean).

Leakage: Based on previous study data (BDT-2P00116) where leakage was greater than or equal to 1.5U was observed in 66/298 (22.1%) of injections performed with Artsana 34G, in 25/299 (8.4%) of injections performed with Comfort EZ 33G, in 19/296 (6.4%) of injections performed with Artsana 33G and in 3/297 (1%) of injections performed with BD Nano™ PRO, a simulation was performed (code found in SVN repository under DBC-18PENDL01/Sample Size/Bayesian prior proportion.R) indicating that 798 injections with BD Nano™ PRO and 266 injections per each comparator would provide >90% power to show BD Nano™ PRO superiority to each comparator. So the number of subjects needed is 133.
A 10% buffer was added (to compensate for subject attrition or unusable data), leading to a planned enrollment number of 146 subjects.

4 Intended Statistical Software

This document was generated with R version 3.5.1 (2018-07-02) and the following packages (version) were used: assertthat (0.2.0), base (3.5.1), BDbasics (0.2.4), bindr (0.1.1), bindrcpp (0.2.2), colorspace (1.3.2), compiler (3.5.1), crayon (1.3.4), datasets (3.5.1), dplyr (0.7.6), ggplot2 (3.1.1), glue (1.3.0), graphics (3.5.1), grDevices (3.5.1), grid (3.5.1), gtable (0.2.0), lattice (0.20.35), lazyeval (0.2.1), magrittr (1.5), methods (3.5.1), munsell (0.5.0), nlme (3.1.137), pillar (1.3.0), pkgconfig (2.0.2), plyr (1.8.4), purrr (0.2.5), R6 (2.2.2), Rcpp (0.12.18), reshape2 (1.4.3), rJava (0.9.10), rlang (0.2.2), scales (1.0.0), stats (3.5.1), stringi (1.1.7), stringr (1.3.1), tibble (1.4.2), tidyselect (0.2.4), tools (3.5.1), utils (3.5.1), withr (2.1.2), xlsx (0.6.1), xlsxjars (0.6.1), xtable (1.8.3).

The analysis of this study will be conducted within the same environment or using more recent versions.

5 Data

5.1 Database Information

The input data will consist in several csv (comma separated values) files exported from Clindex.

Files will be saved in
https://svn.bdx.com:8443/svn/stats_and_dm/DM and Stats Outputs/DBC/DBC-18PENDL02/Data
and read directly into R for analysis.

5.2 Analysis Population Set(s)

All data collected will be analyzed and reviewed for possible exclusion based on significant outliers or protocol deviations.

Injections where bleeding was observed will not be used in the leakage analyses.

Analyses of relative data will only include pairs where both injections were completed.

Demographic information and Diabetes history collected for all subjects randomized will be tabulated.

Data from all subjects will be included in the summary of safety parameters.

6 Statistical Analysis / Calculations

6.1 Derived Variables

6.1.1 Relative VAS Scale

After completion of each pair of injection, subjects will be asked to compare pain between the pen needles using a 150mm relative VAS Scale. Marks made on the 150mm relative VAS Scale are read using a 0 - 20 grid and the resulting discrete scores entered into the database. The results will be transformed to a [-75mm, 75mm] scale for analysis and reporting, where positive scores will reflect less pain for BD Nano Pro and negative scores will reflect less pain for comparator pen needle.

Subjects will draw a vertical line on a relative VAS scale for each pair of injections, to indicate their relative pain perception for the pen needle used first or second in the pair. A vertical line drawn to the left of the center mark indicates that the 1st injection was less painful. A vertical line drawn to the right of the center mark indicates that the 2nd injection was less painful. A vertical line drawn at the center mark indicates no difference. Figure 1 shows an example of a 150mm (may not be to scale) relative VAS scale.

Figure 1: VAS Scale for Injection Pain

The scores are entered into the database on a discrete 0 – 20 scale. These scores will be transformed to a 150mm VAS on a [-75mm, 75mm] scale as follows:

Let $Y_{recorded}$ $(= 0, 1, \cdots, 20)$ be the recorded VAS score, the first transformation for the analysis of VAS score, $Y^*_{analysis}$ (mm), will be calculated as:

$$Y^*_{analysis} = \frac{150}{20} * Y_{recorded} - 75 \tag{1}$$

The sign of the VAS responses $Y^*_{analysis}$ will then be adjusted depending on which pen needle was used in the first and in the second injection, so that positive scores (+) will reflect less pain for BD Nano and negative scores (–) will reflect less pain for comparator pen needles. Let $Y_{analysis}$ be the final relative VAS score used for the analysis. Then:

$$Y_{analysis} = \begin{cases} Y^*_{analysis}, & \text{if BD Nano is provided in the } 2^{\text{nd}} \text{ injection} \\ -Y^*_{analysis}, & \text{if BD Nano is provided in the } 1^{\text{st}} \text{ injection} \end{cases} \tag{2}$$

6.1.2 Leakage Scale

Study Staff will use the provided materials and scale to absorb leakage from the pen needle tip and injection site to measure the amount of leakage. Leakage will be considered to be present if measurement is equivalent to or greater than 5% of dose (equivalent to equal to or greater than 1.5U of U100 insulin (or 0.015g)). A binary leakage variable will be created with the equation below:

$$Y_{Leakage} = \begin{cases} \text{Yes}, & \text{if recorded leakage} \geq 0.015\text{g} \\ \text{No}, & \text{if recorded leakage} < 0.015\text{g} \end{cases} \tag{3}$$

6.1.3 Injection force

Injection force will be evaluated after each pair of injections using a 5-point Likert scale and the results will be converted to ratings of -2 to 2 as below:

$$Y^*_{Injectionforce} = \begin{cases} -2, \text{ if 1st injection significantly less thumb force} \\ -1, \text{ if 1st injection slightly less thumb force} \\ 0, \text{ if no difference} \\ 1, \text{ if 2nd injection slightly less thumb force} \\ 2, \text{ if 2nd injection significantly less thumb force} \end{cases} \tag{4}$$

The sign of the injection force responses $Y^*_{Injectionforce}$ will then be adjusted depending on which pen needle was used in the first and in the second injection, so that positive scores (+) will reflect less thumb force for BD Nano and negative scores (–) will reflect less thumb force for comparator pen needles. Let $Y_{Injectionforce}$ be the final injection force score used for the analysis. Then:

$$Y_{Injectionforce} = \begin{cases} \mathrm{Y}^*_{\mathrm{Injectionforce}}, \text{ if BD Nano is provided in the } 2^{\mathrm{nd}} \text{ injection} \\ -\mathrm{Y}^*_{\mathrm{Injectionforce}}, \text{ if BD Nano is provided in the } 1^{\mathrm{st}} \text{ injection} \end{cases} \tag{5}$$

The responses will also be converted to 3 categories: favoring comparator pen needle (negative ratings), no difference (0 ratings) and favoring BD Nano™ PRO (positive ratings) with the equation below:

$$Y_{Injectionforce(categorical)} = \begin{cases} \text{Comparator pen needle with less injection force if recorded rating } < 0 \\ \text{No difference, if recorded rating } = 0 \\ \text{BD Nano with less injection force if recorded rating } > 0 \end{cases} \tag{6}$$

6.2 Analysis Method

This section provides a detailed description of the statistical analysis that will be performed in this study.

Unless otherwise stated, all the statistical tests are two-sided at a significance level of 5%.

Summary statistics (number of observations, mean, 95% CI for mean, median, standard deviation and range) for all quantitative responses will be presented in tables. Frequency tables with number of observations, percentage of total will be created for all discrete responses. If a modeling approach is applied, the fitted mean with 95% CI will be presented in tables.

Bar plots may be provided for some responses.

6.2.1 Analysis of Injection pain

For each comparator PN, a two-sided 95% confidence intervals will be calculated for the average rating. A modeling approach including data from all pairs of injections (all comparator PN included) will be used to analyze the data and estimate average ratings for each comparator PN adjusting for the pair order effect, BD order effect within pair (due to the often-observed bias towards favoring the last pen needle used in a pair), abdomen site effect, comparator PN effect and random subject effect. The interaction of PN and clinical site will be verified. If the interaction is significant, multiple comparisons for site difference by each PN will be conducted and results will be presented by site for PNs with significant site difference. If the interaction is not significant, it will be dropped from the model and clinical site will be included as main effect. If the site difference is significant, results will be presented by site for each PN. Otherwise, the site effect will be dropped from the model. 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.

```
> ############
> ## Example R code to fit a linear model
> ############
> ##
> ## fitting the model
> library(lme4)
> model.fit=lmer(vas_analysis ~ Comparator*Site + BD_NANO_ORDER + PAIR_ORDER
+                + ABDOMEN_SITE +(1|SUBJ_ID),
+                data=dataset, na.action=na.omit)
>
```

```
> ## Example for estimated pen needle subgroup means (Site effect not significant)
> ##    if the lower CL is > -10, non-inferiority is satisfied
> ##    if the lower CL is > 0, superiority is satisfied
> library(emmeans)
> emmeans(model.fit, ~Comparator)
```

```
 Comparator           emmean       SE     df  lower.CL upper.CL
 Artsana 33G        26.87836 5.747502 140.26 15.515420 38.24129
 Artsana 34G        20.09732 7.841233 139.57  4.594362 35.60027
 Simple Diagnostics 22.40372 6.075449 140.25 10.392416 34.41502

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95
```

6.2.1.1 Additional analysis

Given that there is no significant site effect and no significant difference between any comparator PNs, data from DBC-18PENDL02 and DBC-18PENDL01 will be combined for analysis. An overall result combining all comparators in the two studies will be presented.

6.2.2 Analysis of Injection force

For each comparator PN, the responses in 5-point Likert scale will be converted to ratings of -2 to 2 (where positive ratings favor BD, see Section 6.1.3) and a two-sided 95% confidence interval will be calculated for the average rating. A modeling approach including data from all pairs of injections (all comparator PN included) will be used to analyze the data and estimate average ratings for each comparator PN adjusting for the pair order effect, BD order effect within pair (due to the often-observed bias towards favoring the last pen needle used in a pair), abdomen site effect, comparator PN effect and random subject effect. The interaction of PN and clinical site will be verified If the interaction is significant, multiple comparisons for site difference by each PN will be conducted and results will be presented by site for PNs with significant site difference. If the interaction is not significant, it will be dropped from the model and clinical site will be included as main effect. If the site difference is significant, results will be presented by site for each PN. Otherwise, the site effect will be dropped from the model.

If the lower bound of the CI for the average rating is $>$ 0mm, we can conclude in superiority.

Responses will also be converted to 3 categories: favoring comparator pen needle (negative ratings), no difference (0 ratings) and favoring BD Nano™PRO (positive ratings) (see Section 6.1.3). The difference in percentage of responses with a preference for BD Nano vs each comparator pen needle will be calculated by Bayesian approach, adjusting for the "no preference" category.

6.2.2.1 Additional analysis

Given that there is no significant site effect and no significant difference between any comparator PNs, data from DBC-18PENDL02 and DBC-18PENDL01 will be combined for analysis. An overall result combining all comparators in the two studies will be presented.

6.2.3 Analysis of Needle Bending and Leakage

If there is a sufficient number of occurrences for a modeling approach, analysis will be performed using a binary logistic regression with random subject effect and fixed pen needle type effect, pair order effect,

PN order effect within pair and abdomen site effect. The interaction of PN and clinical site will be verified. If the interaction is significant, multiple comparisons for site difference by each PN will be conducted and results will be presented by site for PNs with significant site difference. If the interaction is not significant, it will be dropped from the model and clinical site will be included as main effect. If the site difference is significant, results will be presented by site for each PN. Otherwise, the site effect will be dropped from the model. The average difference in percentage of occurrence with BD PN and each comparator pen needle will be calculated with 95% confidence interval and assessed for statistical significance. The upper bound of the confidence interval will be compared to 0: superiority will be concluded given that the upper bound of the 95% confidence interval for the difference in proportions is $< 0\%$.

If a modeling approach cannot be applied, a proportion test will be used to detect the difference in percentage of occurrence between sites for each PN. If there is no significant difference, the difference in percentage of occurrence with BD PN and each comparator pen needle will be calculated with 95% confidence interval (Score method) and assessed for statistical significance.

```
> ############
> ## Example R code to fit a logistic regression model
> ############
> ##
> ## fitting the model
> library(lme4)
> model.fit=glmer(leakage ~ PN*Site +PN_ORDER+ PAIR_ORDER + ABDOMEN_SITE
+                 +(1|SUBJ_ID),
+                 data=dataset, na.action=na.omit, family="binomial",
+                 control = glmerControl(optimizer = "bobyqa"),nAGQ = 10)
> library(emmeans)
> emmeans(model.fit, ~PN)
```

```
PN                    emmean       SE  df asymp.LCL asymp.UCL
BD Nano            0.07942998 13925529 Inf -27293535  27293535
Artsana 33G        0.07942595  8632818 Inf -16920013  16920013
Artsana 34G        0.07944491 11568566 Inf -22673973  22673973
Simple Diagnostics 0.07940803 12153341 Inf -23820110  23820111

Results are given on the logit (not the response) scale.
Confidence level used: 0.95
```

6.2.3.1 Additional analysis

Given that there is no significant site effect for DBC-18PENDL02, no significant difference for BD PN between DBC-18PENDL02 and DBC-18PENDL01, and no significant difference between any comparator PNs, data from DBC-18PENDL02 and DBC-18PENDL01 will be combined for analysis. An overall result combining all PNs in the two studies will be presented.

6.2.4 Analysis of Exploratory Objectives (Delivery time, Total injection time, Needle Breaking, and Non-Comparative Questionnaire)

6.2.4.1 Delivery time and Total injection time

A mixed effect model will be used (fixed effects of pen needle type, abdomen site, order of pair, order of pen needle within pair and random subject effect) to estimate average difference (BD Nano PN - each comparator PN) in delivery time and total injection time. The interaction of PN and clinical site will be verified. If the interaction is significant, comparison results will be presented by site. If the interaction is not significant, it will be dropped from the model and clinical site will be included as main effect. If the site difference is significant, mean delivery time and mean total injection time will be presented by site for each PN. Otherwise, the site effect will be dropped from the model. A Box-Cox transformation might be used to normalize the data if necessary. The upper bound of the confidence interval will be compared to 0: superiority will be concluded given that the upper bound of the 95% interval for the average difference is < 0 seconds.

Given that there is no significant site effect for DBC-18PENDL02, no significant difference for BD PN between DBC-18PENDL02 and DBC-18PENDL01, and no significant difference between any comparator PNs, data from DBC-18PENDL02 and DBC-18PENDL01 will be combined for analysis. An overall result combining all PNs in the two studies will be presented.

6.2.4.2 Needle Breaking

The number and proportion of needle breaking occurence for each pen needle type will be summarized. In addition, a 95% confidence interval for difference in proportions between BD Nano PN and each comparator PN will be calculated using the score method for independent proportions. Site effect will be verified in a similar way with needle bending.

6.2.4.3 Non-Comparative Questionnaire

All the responses from Non-Comparative Questionnaire will be summarized with number and percentage of each option. Data from DBC-18PENDL02 and DBC-18PENDL01 will be combined for analysis if possible.

7 Safety Analysis

Data listings will be provided for any adverse events and serious adverse events in Appendix. The events will also be summarized descriptively per pen needle type. No safety analysis is planned.

8 Example Reports

This section provide examples of tables and graphical representations that will be provided in the study statistical report. These table examples were generated using the sample data available from the data base test framework which do not provide an exhaustive or representative example of the values and levels that will be obtained in the study. They are intended to provide illustrative examples of the tables and figures that will be included in the final statistical analysis report.

8.1 Study Execution

The number of subjects enrolled, randomized, withdrawn, who completed and who are excluded will be provided as in Table 2. More details on specific data may be provided in Summary Statistics and Appendix.

8.1.1 Analysis Population Set(s)

Table 1: Population Disposition (Example only)

Subject.Population	N	Comments
Subjects Enrolled	252	none
Subjects who did not meet I/E Criteria	6	none
Subjects Randomized	245	none
Subjects Withdrawn	5	none
Subjects who Completed the Study	240	none
Subjects Excluded from Analysis	1	Give Reasons

Table 2: Number of completed pairs of injection per Comparator PN (Example only)

Comparator	N.pairs
Artsana 33G	265
Artsana 34G	265
Simple Diagnostics	265

8.1.2 Data Exclusions

All exclusions will be listed with reason(s) for exclusion.

8.1.3 Executive Summary

A high level summary will be provided for each objective/endpoint (example below).

Primary Objective (examples only):

- *Injection Pain:* The lower bound of the CI for the average relative pain comparison between BD Nano™ PRO and Artsana Insupen® 33G met both non-inferiority and superiority criteria.

Secondary Objectives (examples only):

- *Injection force:* The lower bound of the CI for the average difference in rating of BD Nano™ PRO and Artsana Insupen® 33G injection force met the superiority criterion.
- *Needle Bending:* The upper bound of the CI for the average difference in percentage of needle bending occurrence with BD Nano™ PRO and Artsana Insupen® 33G met the superiority criterion.
- *Leakage:* The upper bound of the CI for the average difference in percentage of leakage occurrence with BD Nano™ PRO and Artsana Insupen® 33G met the superiority criterion.

In addition, a summary table for all primary and secondary objectives will be presented as in Table 3 (Example only). A blue check mark (✔) indicates that the acceptance criterion is met, while a red X mark (✖) indicates that the acceptance criterion is not met.

Table 3: Results Summary of primary and secondary objectives (Example only)

Objective	Comparison	
Primary Objective		
Injection Pain (Non-inferiority)	BD Nano vs Artsana 33G	✔
Injection Pain (Non-inferiority)	BD Nano vs Artsana 34G	✔
Injection Pain (Non-inferiority)	BD Nano vs Simple Diagnostics	✔
Secondary Objective		
Injection Pain (Superiority)	BD Nano vs Artsana 33G	✖
Injection Pain (Superiority)	BD Nano vs Artsana 34G	✖
Injection Pain (Superiority)	BD Nano vs Simple Diagnostics	✖
Injection force	BD Nano vs Artsana 33G	✔
Injection force	BD Nano vs Artsana 34G	✔
Injection force	BD Nano vs Simple Diagnostics	✔
Needle Bending	BD Nano vs Artsana 33G	✔
Needle Bending	BD Nano vs Artsana 34G	✔
Needle Bending	BD Nano vs Simple Diagnostics	✔
Leakage	BD Nano vs Artsana 33G	✔
Leakage	BD Nano vs Artsana 34G	✔
Leakage	BD Nano vs Simple Diagnostics	✔

8.2 Analysis and Results

8.2.1 Injection Pain

Summary statistics for the VAS scale will be presented as in Table 4.

The results for average relative VAS Score for BD Nano™ PRO vs comparator pen needle will be evaluated as presented in Table 5.

Table 4: Summary Statistics for observed 150mm Relative VAS Scores (Example only)

Comparison	N	Mean	Std. Dev.	Mean 95% CI	Median	Median 95% CI	Range
BD Nano vs Artsana 33G	13	12.12	44.00	(-74.13, 98.36)	15.00	(-71.25, 101.25)	-75, 67.5
BD Nano vs Artsana 34G	12	0.00	27.14	(-53.19, 53.19)	-7.50	(-60.69, 45.69)	-37.5, 45
BD Nano vs Simple Diagnostics	9	-10.00	41.59	(-91.52, 71.52)	-22.50	(-104.02, 59.02)	-52.5, 60

Table 5: Fitted Average Relative VAS score for BD Nano vs comparator pen needles (Example only)

Comparison	Fitted Mean	CI	Non-Inferiority Conclusion (Lower bound CI > -10)	Superiority Conclusion (Lower bound CI > 0)
BD Nano vs Artsana 33G	28.3	(17.1, 39.4)	TRUE	TRUE
BD Nano vs Artsana 34G	19.2	(4.1, 34.4)	TRUE	TRUE
BD Nano vs Simple Diagnostics	26.1	(10.3, 42)	TRUE	TRUE

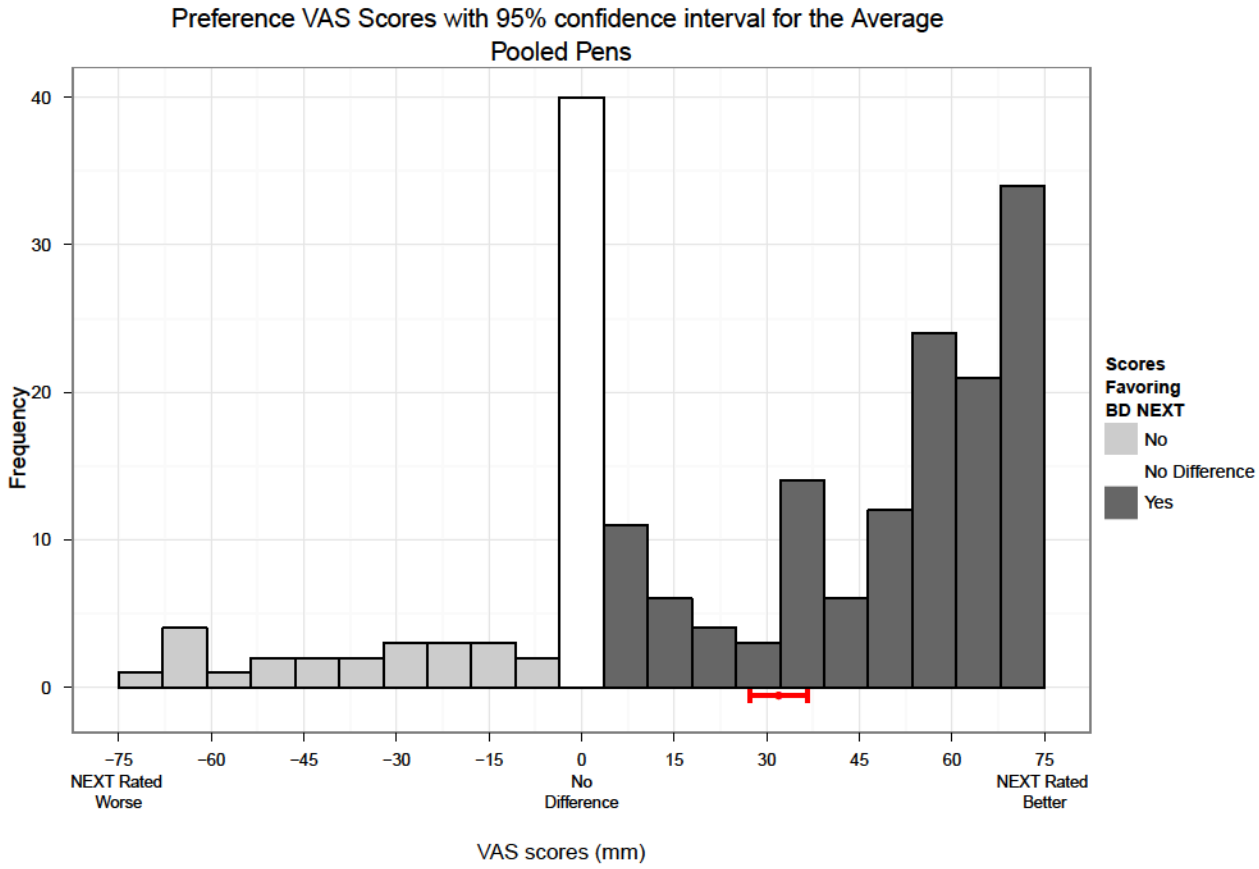

Figure 2: Distribution of relative VAS scores with average and confidence interval per pen needle group and overall. Positive scores indicate that BD Next was preferred and negative scores indicate that the Current/Assigned PN was preferred. Note: This example graph comes from a study with different PN. Results for this study will reflect BD Nano performance.

8.2.2 Injection force

The distribution of the ratings of injection force for BD Nano vs each comparator pen needle will be presented as in Table 6 and Figure 3. Summary statistics for the ratings of injection force will be presented as in Table 7.

The results of average ratings will be evaluated as presented in Table 8.

Table 6: Distribution of injection force ratings (BD Nano vs Artsana 33G) (Example only)

Rating	n (%)
-2 (Artsana 33G significantly less thumb force)	66 (20.0%)
-1 (Artsana 33G slightly less thumb force)	66 (20.0%)
0 (No Difference)	66 (20.0%)
1 (BD Nano slightly less thumb force)	66 (20.0%)
2 (BD Nano significantly less thumb force)	66 (20.0%)
Total	330
All Rating: >0	132 (43.9%)

Table 7: Summary Statistics for observed ratings of injection force (Example only)

Comparison	N	Mean	Std. Dev.	Mean 95% CI	Median	Median 95% CI	Range
BD Nano vs Artsana 33G	266	1.4	0.1	[-0.1, 2]	1.5	[-0.1, 2]	-2, 2
BD Nano vs Artsana 34G	266	1.5	0.1	[-0.1, 2]	1.5	[-0.1, 2]	-2, 2
BD Nano vs Simple Diagnostics	266	1.6	0.1	[-0.1, 2]	1.5	[-0.1, 2]	-2, 2

Figure 3: Summary for observed ratings of injection force per pen needle type (Example only)

Table 8: Fitted average ratings of injection force (Example only)

Comparison	Mean	CI	Superiority Conclusion (Lower bound CI > 0)
BD Nano vs Artsana 33G	1.30	[-0.1, 2]	Fail
BD Nano vs Artsana 34G	1.40	[0.1, 2.5]	Pass
BD Nano vs Simple Diagnostics	1.60	[0.1, 2.8]	Pass

The difference in percentage of responses with a preference for BD vs each comparator pen needle will be presented as in Table 9.

Table 9: Difference in Percentage of responses with a preference for BD Nano vs comparator PN (Example only)

Comparison	percentage of responses with a preference for BD Nano	percentage of responses with a preference for comparator	Difference in Percentage (BD Nano - comparator)	95% CI for Difference
BD Nano vs Artsana 33G	45.5%	40.0%	5.5%	[2.1%, 6.8%]
BD Nano vs Artsana 34G	55.5%	30.0%	25.5%	[12.2%, 36.8%]
BD Nano vs Simple Diagnostics	49.5%	35.0%	14.5%	[10.1%, 18.8%]

8.2.3 Needle Bending

Summary statistics for needle bending will be presented as in Table 10.

The results of difference in percentage of needle bending will be evaluated as presented in Table 11.

Table 10: Observed percentage of Needle Bending (Example only)

Pen Needle	Needle bending	95% CI
BD Nano	2/266 (0.8%)	[0.1%, 1.5%]
Artsana 33G	5/266 (1.9%)	[1.2%, 2.6%]
Artsana 34G	5/266 (1.9%)	[1.2%, 2.6%]
Simple Diagnostics	5/266 (1.9%)	[1.2%, 2.6%]

Table 11: Difference in Percentage of Needle Bending based on modeling analysis. (Example only)

Comparison	Difference in Percentage of Needle bending	95% CI for Difference	Superiority (Upper bound <0)
BD Nano vs Artsana 33G	-1.1%	[-3.2%, 0.8%]	Fail
BD Nano vs Artsana 34G	-1.1%	[-3.2%, 0.8%]	Fail
BD Nano vs Simple Diagnostics	-1.1%	[-3.2%, 0.8%]	Fail

8.2.4 Leakage from Injection Site

Summary statistics for leakage from injection site will be presented as in Table 12. The distribution of leakage from injection site will be presented as in Figure 4.

The leakage on a binary scale will also be presented and analyzed as in Section 8.2.3.

Table 12: Summary Statistics for leakage from injection site (Example only)

Pen needle	N	Mean	Std. Dev.	Median	Range
BD Nano	3	0.0176	0.0189	0.0185	0.0112, 0.0298
Artsana 33G	5	0.0234	0.0147	0.0226	0.0132, 0.0342
Artsana 34G	6	0.0234	0.0147	0.0226	0.0132, 0.0342
Simple Diagnostics	6	0.0234	0.0147	0.0226	0.0132, 0.0342

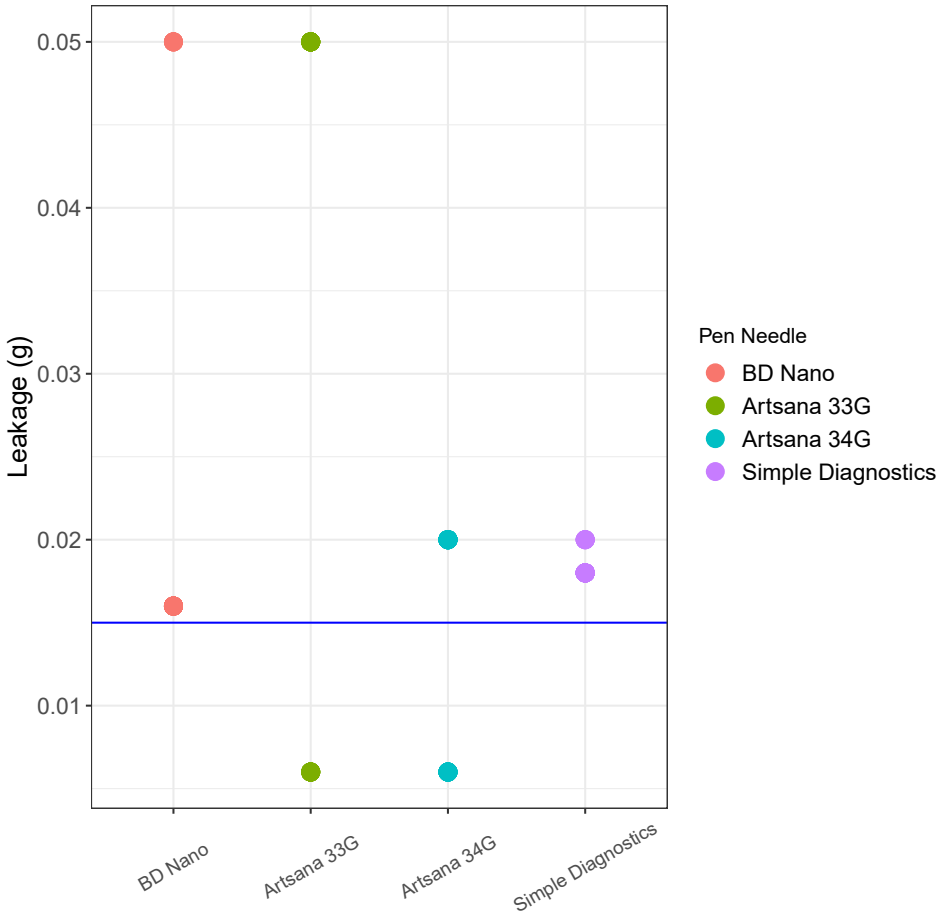

Figure 4: Leakage from the injections per pen needle type. The blue line represents the threshold for leakage (0.015g).

8.2.5 Exploratory Objectives

Patient end needle breaking will be summarized as in Section 8.2.3.

Summary statistics for delivery time and total injection time will be presented as in Table 13. The average difference (BD PN - comparator PN) in delivery time and total injection time will be evaluated as presented in Table 14.

Summary statistics for Non-Comparative Questionnaire will be presented as in Table 7.

Table 13: Summary Statistics for delivery time (Example only)

Pen Needle	N	SD	Mean	Median	Range
BD Nano	31	40.52	142.03	142.00	90, 274
Artsana 33G	31	63.90	165.84	140.00	91, 362
Artsana 34G	29	46.64	150.41	137.00	84, 324
Simple Diagnostics	30	56.14	171.20	150.00	103, 322

Table 14: Mean difference of Delivery time and Total injection time with confidence interval (reciprocal of number of seconds) between BD Nano and Artsana 33G. The last column indicates whether superiority was met or not. (Example only)

	Mean difference	95% Lower bound	P value	Superiority (Lower bound >0)
Delivery time	-0.000739	-0.001658	0.113	Fail
Total injection time	0.000452	-0.000377	0.279	Fail

8.3 Demographics and Diabetes History

Table 15: Subject Demographics (Example only)

Characteristic		Results
Gender		
	Female	94 (50.8%)
	Male	91 (49.2%)
Age		
	Mean	55.8
	95% Mean CI	53.9, 57.7
	SD	13.0
	Min, Max	20, 76
	Observation Count	183
	Missing Count	2
	Total Count	185

Table 16: Distribution of Type of Diabetes (Example only)

Characteristic		Results
Diabetes Type		
	Type II	152 (84.4%)
	Type I	28 (15.6%)
	Missing	2

Table 17: Diabetes History (Example only)

Characteristic	Results
Diagnosed year	
Mean	14.2
95% Mean CI	12.8, 15.6
SD	9.4
Min, Max	1, 54
Total Count	182
Injection Times per day	
once	74 (40.7%)
four	36 (19.8%)
twice	31 (17.0%)
five or more	19 (10.4%)
NA - injects non-insulin only	11 (6.0%)
three	11 (6.0%)
Pen needle used	
BD Nano 32Gx4mm	66 (36.5%)
NovoFine 32Gx6mm	33 (18.2%)
Other 32G	24 (13.3%)
Other 31Gx5mm	22 (12.2%)
NovoTwist 32Gx5mm	20 (11.0%)
NovoFine Plus 32Gx4mm	14 (7.7%)
Owen Mumford PenTips 32Gx4mm	2 (1.1%)
Missing	1
Injection site used	
Abdomen	158 (87.3%)
Thigh	14 (7.7%)
Arm	7 (3.9%)
Buttocks	1 (0.6%)
Other	1 (0.6%)
Missing	1

9 Appendix

9.1 Discontinued Data

The Table 18 shows the detailed list of discontinued subjects.

Table 18: Details of Discontinued Subjects (Example only)

Subject ID	Completion Date	Discontinuation Time	Reason for Discontinuation	Details
R003	January 3, 2018	After initiation of study procedure/ intervention	Other	Subject decided not continue to participate
R067	February 7, 2018	Before any study procedure/ intervention	Did not meet criteria (Screen Failure)	
R114	February 19, 2018	After initiation of study procedure/ intervention	Administrative Issue	Detail of reason for discontinuation

9.2 Missing Data

All the Missing data will be listed.

9.3 Adverse Events

Data listings will be provided for any adverse events and serious adverse event in Table 19. Adverse events will be summarized descriptively by pen needle in Table 20 and 21.

Table 19: Data listing for adverse events (Example only)

Random ID	PN Used	Seriousness	Severity	Relation to product	Contribution of product malfunction	Relation to protocol	Description
R055	BD Nano	Serious	Moderate	Related	Yes	Not related	adverse event to be described
R001	Artsana 33G	Serious	Mild	Unlikely related	No	Possibly related	adverse event to be described
R099	Artsana 33G	Serious	Severe	Possibly related	Yes	related	adverse event to be described

Table 20: Summary of Adverse Events: Relationship to product (Example only)

Pen Needle	Number of events	Number of Subjects	Not related	Unlikely related	Possibly related	Related
BD Nano	5	2	2	1	1	1
Artsana 33G	0	0	0	0	0	0
Artsana 34G	0	0	0	0	0	0
Simple Diagnostics	0	0	0	0	0	0

Table 21: Summary of Adverse Events: Relationship to protocol / procedure (Example only)

Pen Needle	Number of events	Number of Subjects	Not related	Unlikely related	Possibly related	Related
BD Nano	5	2	2	1	1	1
Artsana 33G	0	0	0	0	0	0
Artsana 34G	0	0	0	0	0	0
Simple Diagnostics	3	3	0	1	0	2