Statistical Analysis Plan

Protocol Number/version	DBC-17NUCLS07 (Version 5.0 December 20, 2017 (Amendment 4))
Protocol Title	Nucleus Claims Study: Evaluating the User Performance and Experience of BD Nucleus Pen Needle vs. Commercially Available Pen Needle
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Approval

Individual or Function	Name	Signature	Date
Statistics Manager	Julie Bérubé	This document is signed electronically in the eTMF system	
Study Manager	Lydia Blank	This document is signed electronically in the eTMF system	
Medical Affairs, Team Representative	Shahista Whooley	This document is signed electronically in the eTMF system	
WW Director Stats & Stats Programming	Paula Johnson	This document is signed electronically in the eTMF system	

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1 List of Abbreviations and Definitions

AE	Adverse Events
BD	Becton Dickinson & Company
BG	Blood Glucose
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report/ Record Form
FDA	Food and Drug Administration
G	Gauge
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
INJ	Injection
ITT	Intent-to-treat
mm	Millimeter
NI	Non-Inferiority
PN	Pen Needle
PP	Per-Protocol
SAE	Serious Adverse Events
SD	Standard Deviation
VAS	Visual Analog Scale

2 Executive Summary

Summary statements will be made to show the results of both non-inferiority tests and the statistical conclusions per endpoint. Summary tables will also be provided.

3 Background and Study Description

3.1 Study Background

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).

3.2 Study Objectives

3.2.1 Primary Objectives

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

3.2.2 Secondary Objectives

1. For each individual study group, compare user preference for the BD Nucleus pen needle vs. the subjects' current commercially available pen needle.
2. For all study groups combined and each individual study group, compare the user experience with the BD Nucleus pen needle and the subjects' current commercially available pen needle for component preference.
   (a) Outer Cover Handling
   (b) Inner Shield Handling
   (c) Hub Comfort
3. For all study groups combined and each individual study group, compare the user experience with the BD Nucleus pen needle and the subjects' current commercially available pen needle for the following:
   (a) Overall Comfort
   (b) Anxiety associated with a needle stick injury
   (c) Injection Pain
   (d) Bruising
   (e) Bending
   (f) Injection site Bleeding
   (g) Ease of use
   (h) Leakage from the injection site

3.2.3 Exploratory Objectives

1. 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
2. For all study groups combined, Pen Needle breakage will be monitored.
3. A subgroup with Asian ethnicity and all study groups combined, will also be evaluated for the objectives listed in Primary and Secondary Objectives.

3.3 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. BD Nucleus will be compared to four groups of pen needles:

- Group 1: BD Nano (32Gx4mm)
- Group 2: NovoFine (32Gx6mm)
- Group 3: NovoFine Plus (32Gx4mm) & NovoTwist (32Gx5mm)
- Group 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 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. Subjects 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 subjects 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 (cf. Wash-in randomization schedule):

- 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).

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 (cf. Figure 1). Note that in the following document, "Current PN" and "Current/Assigned PN" are both used interchangeably to refer to the study arm where subjects did not use BD Nucleus PN.

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.

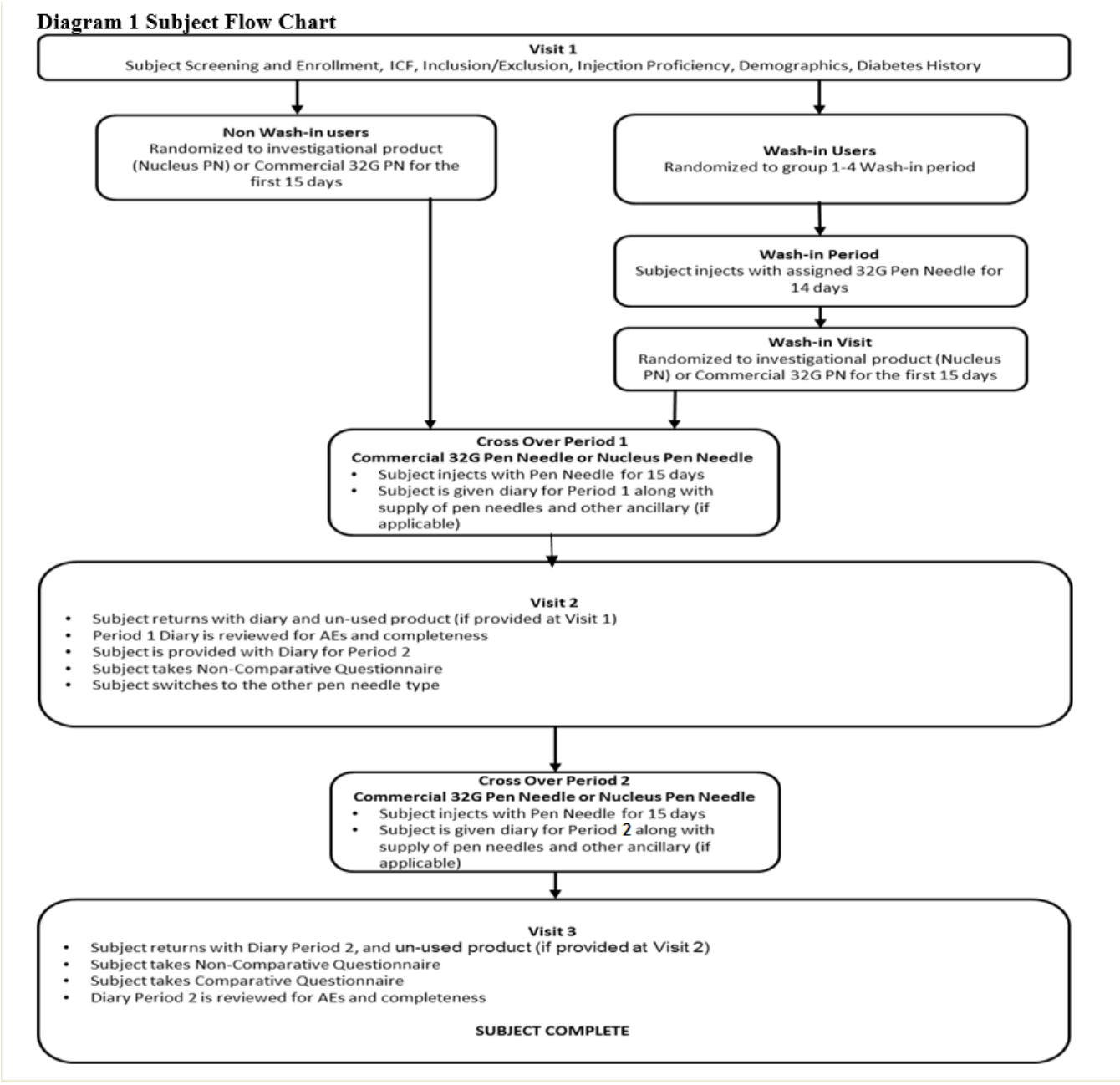

Figure 1: Subject Flow Chart

3.4 Endpoints

3.4.1 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 is labelled "Period 1 pen needle was *strongly* preferred

overall", the 0mm center point is labelled "No preference" and the far right (+75mm) of the scale is labelled "Period 2 pen needle was *strongly* preferred overall". The average rating will be used to assess non-inferiority and superiority.

3.4.2 Secondary Endpoints

- **Overall Comfort, Anxiety Associated with a Needle Stick Injury, Injection Pain, Ease of Use, Outer Cover Handling, Inner Shield Handling, Hub Comfort**: 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. Average ratings will be used to assess non-inferiority and superiority.

- **Needle Bending or Injection Site Bleeding or Bruising**: After each injection, each subject will evaluate his/her perception of each by answering with a "Yes" or "No" response. The difference in percentage of "Yes" responses between the PNs will be used to assess non-inferiority.

- **Leakage**: After each injection leakage will be recorded using the scale below. Recorded leakage will be transformed to Yes/No scale and the difference in percentage of "Yes" responses between the PNs will be used to assess non-inferiority.

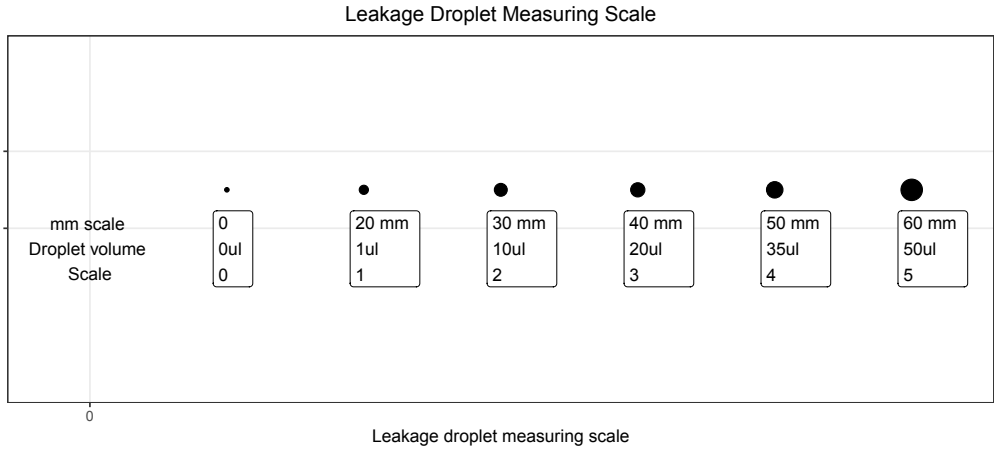

Figure 2: Subject Flow Chart

3.4.3 Exploratory Endpoints

At the end of each study 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?"

- **Outer Cover Removal Force**: The subject will be asked "Did you find the outer cover easy to remove?"

- **Inner Shield Removal Force**: The subject will be asked "Did you find the inner shield easy to remove?"
- **Ease of Insulin Delivery**: The subject will be asked "Were you able to deliver the insulin easily?"

Needle Breaking: After each injection, each subject will evaluate his/her perception by answering with a "Yes" or "No" response. The difference in percentage of "Yes" responses between the PNs will be used as an endpoint.

3.4.4 Safety Endpoints

At second and third visits, presence and severity of any adverse events will be evaluated, recorded, and followed up as required.

3.5 Acceptance Criteria

3.5.1 Primary Objective

Non-Inferiority Criterion (based on relative VAS where -75mm is strongly preferred Current/Assigned and +75mm is strongly preferred Nucleus) is -10mm and the Superiority Criterion is 0mm.

3.5.2 Secondary Objectives

- Overall Comfort, Anxiety Associated with a Needle Stick Injury, Injection Pain, Ease of Use, Outer Cover Handling, Inner Shield Handling, Hub Comfort: Same as for primary objective
- 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.

3.5.3 Exploratory Objectives

No formal acceptance criteria.

4 Sample Size

Based on previous studies, SD for relative VAS is assumed to be 35mm. A sample size of 60 subjects per group has 90% power of passing a 10mm Non-Inferiority (NI) criteria, assuming a true average of 5mm in favor of Nucleus (2-sided 95% CI for the mean). A sample size of minimum 45 subjects per group is sufficient to provide at least 80% power (this lower sample size may be used for Group 2, Group 3 and Group 4). This sample size applies to each subgroup for which a NI (or superiority) claim is desired.

5 Intended Statistical Software

This document was generated with R version 3.3.2 (2016-10-31) and the following packages (version) were used: assertthat (0.1), base (3.3.2), BDbasics (0.1.11), colorspace (1.3.2), datasets (3.3.2), ggplot2 (2.2.0), graphics (3.3.2), grDevices (3.3.2), grid (3.3.2), gtable (0.2.0), lattice (0.20.34), lazyeval (0.2.0), magrittr (1.5), methods (3.3.2), munsell (0.4.3), nlme (3.1.128), plyr (1.8.4), Rcpp (0.12.13), reshape2 (1.4.2), rJava (0.9.8), scales (0.4.1), stats (3.3.2), stringi (1.1.2), stringr (1.1.0), tibble (1.2), tools (3.3.2), utils (3.3.2), xlsx (0.5.7), xlsxjars (0.6.1), xtable (1.8.2).

The study will be conducted within the same environment or more recent versions.

6 Data

6.1 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-17NUCLS07/Data
and read directly into R for analysis.

6.2 Analysis Population Set(s)

Two population will be defined:

- Per-Protocol (PP) Population: Excludes subjects or outcomes based on significant protocol deviations
- Intent-to-Treat (ITT) Population: Includes all randomized subjects, regardless of protocol deviations or whether they followed the randomization.

The primary analyses will be performed on the PP population and all conclusions drawn from those analyses. Analysis based on IIT population will be for information only and presented in Appendix. The number of subjects enrolled, randomized, withdrawn, who completed and who are excluded will be summarized per PP and ITT populations.

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.

Analysis of relative VAS will only include subjects who completed both study periods.

7 Statistical Analysis / Calculations

7.1 Derived Variables

7.1.1 VAS Scale

There is one comparative questionnaire collected at the end of the two study periods. Subjects will be asked questions to compare between the pen needles used in the two periods. The questionnaire is comprised of multiple 150mm relative VAS Scales which are read on a 0 – 20 grid in the database. The results will be transformed for analysis and reporting, to correspond to a [-75mm, 75mm] scale so that positive scores (+) will reflect preference for BD Nucleus and negative scores (–) will reflect preference for the Current/Assigned pen needle.

Subjects will draw a vertical line on each VAS scale relating to each question, to indicate their relative preference for the pen needle used in one period over the other. A vertical line drawn to the left of the center mark indicates that "Period 1 pen needle was *strongly* preferred" and the result will be shown in (–) mm (minimum score -75mm). A vertical line drawn to the right of the center mark indicates that "Period 2 pen needle was *strongly* preferred" and the result will be shown in (+) mm (maximum score +75mm). A vertical line drawn at the center mark indicates "No preference" and is scored as "0". Figure 3 shows an example of a 150mm relative VAS scale.

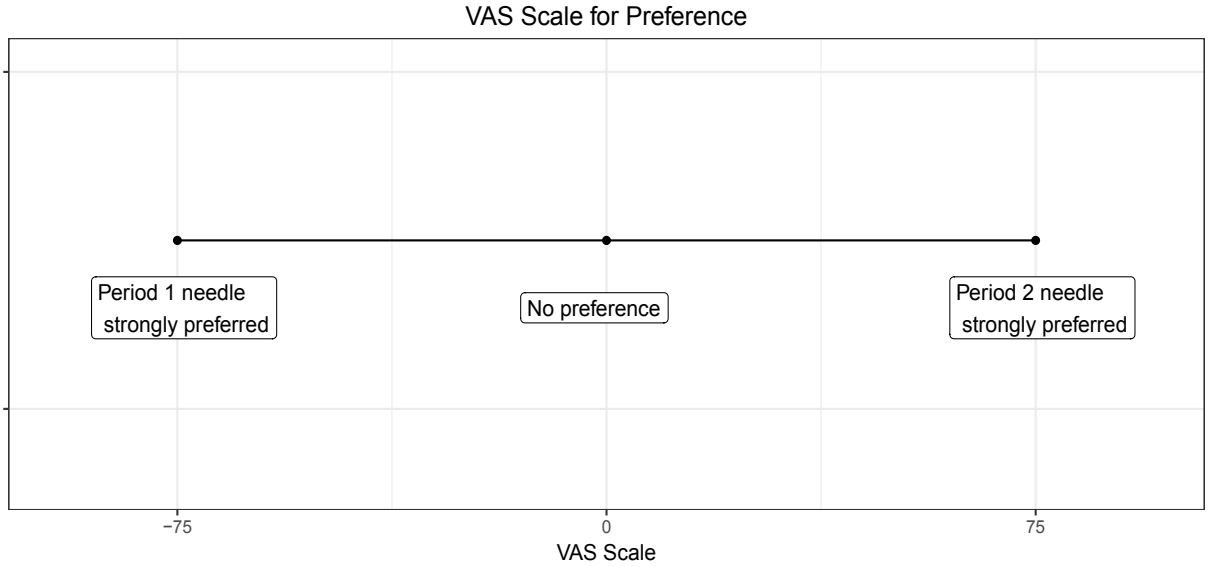

Figure 3: VAS Scale for Preference

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 period, so that the positive scores (+) will reflect preference for BD Nucleus and the negative scores (–) will reflect preference for the current pen needle. Let $Y_{analysis}$ be the final relative VAS score used for the analysis. Then:

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

7.1.2 Leakage Scale

Needle leakage from the injections will be evaluated categorically according the droplet size at 6 different levels. Needle leakage is recorded using the 0 - 5 scale described in Figure 2. A binary leakage variable will be created with the equation below:

$$Y_{leak} = \begin{cases} \text{Yes}, & \text{if recorded leak score } > 0 \\ \text{No}, & \text{if recorded leak score } = 0 \end{cases} \tag{3}$$

7.1.3 Sub grouping Indicators

Indicator variables will be created to identify each of the following:

- Subjects with Asian ethnicity
- Subjects with a wash-in period

7.2 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% and adjustment will be made for multiple comparisons when appropriate.

All the primary and secondary endpoints will also be analyzed as described below for the Asian subpopulation.

7.2.1 Summary Statistics

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. All summary and descriptive statistics will be provided per pen needle group and overall.

Bar plots may be provided for some responses.

7.2.2 Statistical Methods

All Primary and Secondary 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 performed to determine whether it is valid to combine the results from the four study groups 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. This assessment may be performed by including a "wash-in" effect into the analysis model. This is for information only.

A site effect will be investigated and if significant, comparisons between sites will be performed. This is for information only.

7.2.2.1 Analysis of Relative VAS Score

For each outcome measured on a relative VAS, a two-sided 95% confidence intervals will be calculated for the average rating. A modeling approach will be used to adjust for the order effect (because of the often observed bias towards favoring the last PN used). A linear model will be used to evaluate the pen needle group effect on the response to test whether the groups can be combined (a p-value < 0.05 for the pen needle group effect indicates non-poolability). In the model, the order of the pen needles used and the group to which the subject belongs based on their currently used or assigned pen needle will be used as covariates. LS means with CI will be obtained from the model and 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.

Additional analysis: a *wash-in* indicator and an *Asian* indicator may be used to investigate these effects, as well as a site effect.

```
> ############
> ## Example R code to fit a linear model
> ############
> ##
> ## fitting the model
> model.fit=lm(vas_analysis ~ (NUCL_ORDER + PN_GROUP + ASIA)^2 + WASH_IN,
+              data=dataset, na.action=na.omit)
> #ANOVA table
> ## if p-value for PN_GROUP < 0.05, results not poolable across Groups
> anova(model.fit)
```

```
Analysis of Variance Table

Response: vas_analysis
                     Df Sum Sq Mean Sq F value Pr(>F)
NUCL_ORDER            1    192   191.7  0.0928 0.7612
PN_GROUP              3   2757   919.0  0.4446 0.7215
ASIA                  1   3215  3215.0  1.5554 0.2144
WASH_IN               1    751   750.8  0.3632 0.5477
NUCL_ORDER:PN_GROUP   3   3991  1330.3  0.6436 0.5882
NUCL_ORDER:ASIA       1    131   130.8  0.0633 0.8017
PN_GROUP:ASIA         3    308   102.6  0.0496 0.9853
Residuals           139 287317  2067.0
```

```
> ##example contrast for the different pen needle groups
> ##   given results not poolable,
> ##   to identify which groups are not poolable
> ##
> model.fit=lm(vas_analysis ~ NUCL_ORDER + PN_GROUP,
+              data=dataset,
+              na.action=na.omit)
> ##
> library(multcomp)
> confint(glht(model.fit, linfct = mcp(PN_GROUP = "Tukey")))
```

```
         Simultaneous Confidence Intervals

Multiple Comparisons of Means: Tukey Contrasts


Fit: lm(formula = vas_analysis ~ NUCL_ORDER + PN_GROUP, data = dataset,
    na.action = na.omit)

Quantile = 2.5914
```

```
95% family-wise confidence level


Linear Hypotheses:
                       Estimate lwr      upr
Group 2 - Group 1 == 0  -9.0440 -33.6940  15.6060
Group 3 - Group 1 == 0  -2.1486 -27.5651  23.2678
Group 4 - Group 1 == 0  -9.5985 -37.0536  17.8566
Group 3 - Group 2 == 0   6.8954 -21.8716  35.6623
Group 4 - Group 2 == 0  -0.5545 -31.1299  30.0209
Group 4 - Group 3 == 0  -7.4499 -38.6268  23.7269
```

```
> ## Example for estimated pen needle subgroup means
> ##    if the lower CL is > -10, non-inferiority is satisfied
> ##    if the lower CL is > 0, superiority is satisfied
> library(lsmeans)
> lsmeans(model.fit, ~PN_GROUP)
```

```
 PN_GROUP   lsmean       SE  df   lower.CL upper.CL
 Group 1  28.27822 5.634375 148 17.1440031 39.41243
 Group 2  19.23421 7.666839 148  4.0835958 34.38482
 Group 3  26.12959 8.028290 148 10.2647028 41.99447
 Group 4  18.67968 8.960491 148  0.9726509 36.38671

Confidence level used: 0.95
```

7.2.2.2 Needle Bending, Injection site Bleeding and Bruising

For each pen needle group, 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/Assigned PN

Results will be tested for non-inferiority: If the upper bound of the CI is $< 4\%$, we can conclude in non-inferiority.

If results are poolable, results will also be presented for the groups combined. Poolability will be assessed through a mixed effects logistic regression model including a PN group by PN type interaction. If the interaction is significant, results are not poolable and only poolable groups will be presented combined.

```
> ############
> ## Example R code to test the difference in proportion of response
> ############
>
> ## Two-Sample difference in proportion test
>
> propdat <- data.frame(Break=c(45,56),NoBreak=c(780,810))
> row.names(propdat) <- c("BD Nucleus","Comparator")
> propdat$Total <- rowSums(propdat)
> propdat$Proportion <- propdat$Break/propdat$Total
> #
> library(PropCIs)
> ## 95\% confidence interval
> #
> proptestci <- diffscoreci(x1=propdat["BD Nucleus","Break"],
+                           n1=propdat["BD Nucleus","Total"],
+                           x2=propdat["Comparator","Break"],
+                           n2=propdat["Comparator","Total"],
+                           conf.level=0.95)$conf.int
> #
> propest <- propdat["BD Nucleus","Proportion"] -
+   propdat["Comparator","Proportion"]
> #
> #if upper bound of CI < 0.04, NI satisfied
> data.frame(Estimate=propest,
+                    CI = paste0("(",proptestci[1],", ",proptestci[2],")"))
```

```
    Estimate                                          CI
1 -0.01011967 (-0.0330320064995986, 0.0127257649847972)
```

```
> ############
> ## Example R code for poolability testing
> ############
> library(lme4)
> ## mixed effects logistic regression model
> model = glmer(BLEEDING ~DEMO_PN_GROUP*RS_PN + (1 |SUBJ_ID),
+               data=diary, family=binomial,
+               control = glmerControl(optimizer = "bobyqa"))
> library(car)
> #if interaction p-value < 0.05, group results not poolable
> #
```

```
> Anova(model,type="III")
```

```
Analysis of Deviance Table (Type III Wald chisquare tests)

Response: BLEEDING
                       Chisq Df            Pr(>Chisq)
(Intercept)         186.7400  1 < 0.00000000000000022
DEMO_PN_GROUP         3.3702  3              0.337994
RS_PN                 8.8563  1              0.002921
DEMO_PN_GROUP:RS_PN  14.6710  3              0.002120
```

7.2.2.3 Analysis of Leakage

Distribution of leakage scores will be provided and proportion of injections with recorded leakage score >0 will be calculated per Pen Needles in each subgroup. Analysis as in Section 7.2.2.2 will be performed using the proportion of injections with recorded leakage score > 0 as response.

7.2.2.4 Analysis of Exploratory Objectives (Non-Comparative Questionnaire and Needle Breaking)

All the Exploratory binary responses (Yes / No) will be summarized with proportion of "Yes" answers and 95% confidence interval (score method) per pen needle group and overall.

In addition, for each pen needle group, a 95% confidence interval for the Proportion "Yes" with the BD Nucleus PN vs the Proportion "Yes" with the Current/Assigned PN will be calculated using the score method for independent proportions.

8 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 and study group. No safety analysis is planned.

9 Interim Analysis

Interim analyses will be performed for information only with no alpha adjustment.

10 Additional Analysis

A sub-group with Asian ethnicity, all study groups combined, will also be evaluated for the objectives listed in Section 3.2.1 and 3.2.2.

The primary endpoint may also be evaluated within each subgroups based on whether the patients had washout period before randomization.

11 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.

11.1 Study Execution

The number of subjects enrolled, randomized, withdrawn, who completed and who are excluded will be provided as in Table 1. More details on specific data may be provided in Summary Statistics and Appendix.

11.1.1 Analysis Population Set(s)

Table 1: (PP) Population Disposition

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: Population per Subgroup - Randomized Subjects, with or without a wash-in period.

Pen Needle Group	No Wash-in	Wash-In	Overall
Group 1	66 (40.5%)	0 (0.0%)	66 (35.7%)
Group 3	33 (20.2%)	12 (54.5%)	45 (24.3%)
Group 4	28 (17.2%)	10 (45.5%)	38 (20.5%)
Group 2	36 (22.1%)	0 (0.0%)	36 (19.5%)
Total	163	22	185

11.1.2 Data Exclusions

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

11.2 Analysis and Results

11.2.1 Comparative Questionnaire (Relative VAS)

This section applies to all responses recorded on a relative VAS scale.

Summary statistics for each VAS scale will be presented as in Table 3.

The results for average relative VAS Score for BD Nucleus Pen Needle vs Current/Assigned Pen Needle will be evaluated per subgroup as presented in Table 4. The p-value for poolability will be provided in the caption (if the p-value < 0.05, then the results are not poolable across the groups). Results for all subgroups combined will only be presented if groups are poolable, otherwise only poolable groups will be combined. In the example in Table 4, all groups are poolable.

Table 3: Summary Statistics for 150mm Relative VAS Scores

Group	N	Mean	Std. Dev.	Mean 95% CI	Median	Median 95% CI	Q1	Q3	Range
Group 1	13	12.12	44.00	(-74.13, 98.36)	15.00	(-71.25, 101.25)	-15.00	60.00	-75, 67.5
Group 2	12	0.00	27.14	(-53.19, 53.19)	-7.50	(-60.69, 45.69)	-13.12	22.50	-37.5, 45
Group 3	9	-10.00	41.59	(-91.52, 71.52)	-22.50	(-104.02, 59.02)	-52.50	30.00	-52.5, 60
Group 4	10	-15.00	38.41	(-90.28, 60.28)	-37.50	(-112.78, 37.78)	-37.50	20.62	-52.5, 45
Combined	44	-1.88	38.38	(-77.11, 73.36)	-7.50	(-82.73, 67.73)	-37.50	30.00	-75, 67.5

Table 4: Average Relative VAS score for Nucleus vs Comparator PN table per Subgroup and overall (poolable groups). p-value for poolability = 0.7, all groups poolable

Pen Needle Group	Fitted Mean	CI	Non-Inferiority Conclusion (Lower bound CI > -10)	Superiority Conclusion (Lower bound CI > 0)
Group 1	28.3	(17.1, 39.4)	TRUE	TRUE
Group 2	19.2	(4.1, 34.4)	TRUE	TRUE
Group 3	26.1	(10.3, 42)	TRUE	TRUE
Group 4	18.7	(1, 36.4)	TRUE	TRUE
All Groups Combined	23.1	(15.5, 30.7)	TRUE	TRUE

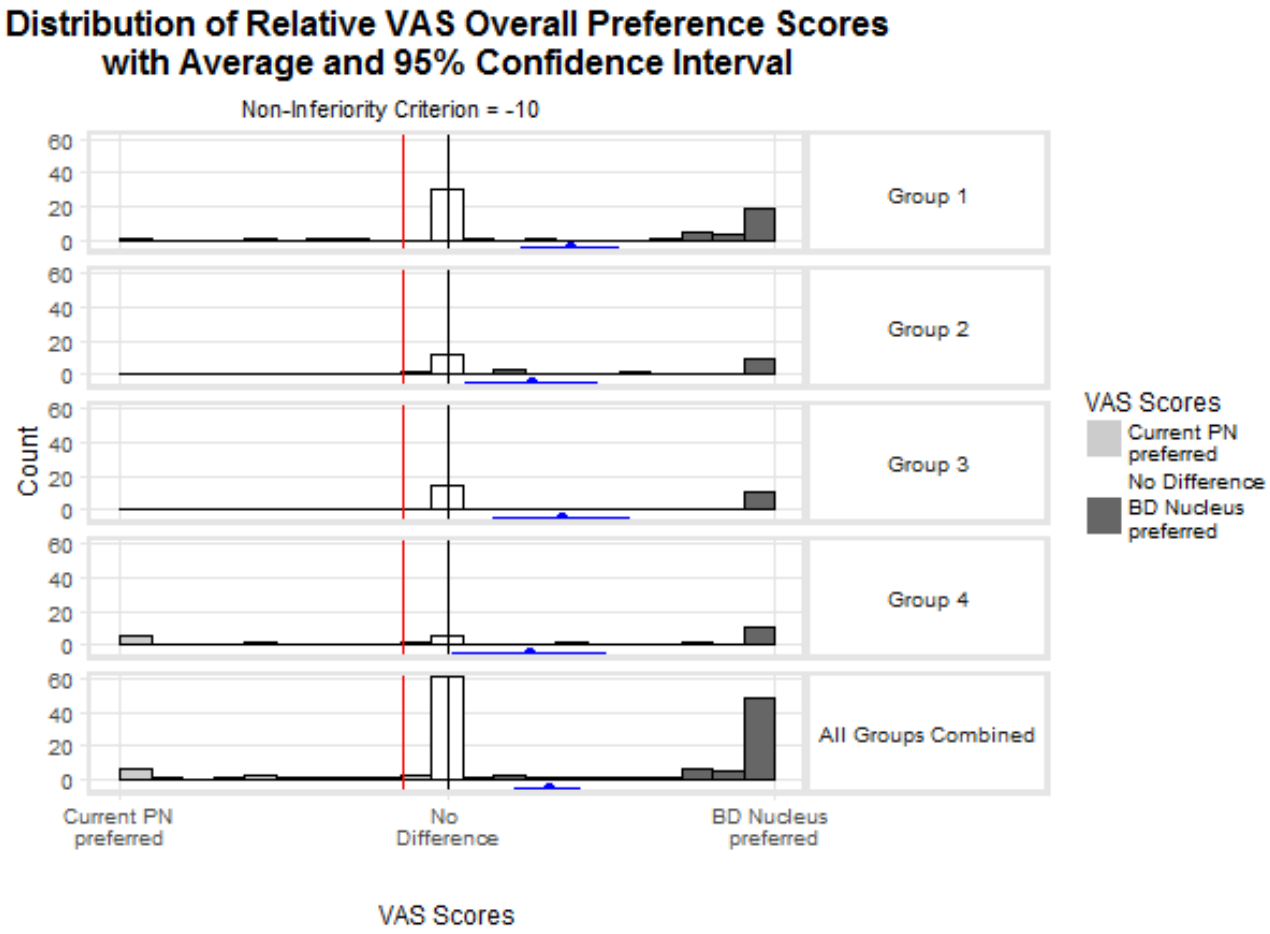

Figure 4: Distribution of relative VAS scores with average and confidence interval per pen needle group and overall. Positive scores indicate that BD Nucleus was preferred and negative scores indicate that the Current/Assigned PN was preferred.

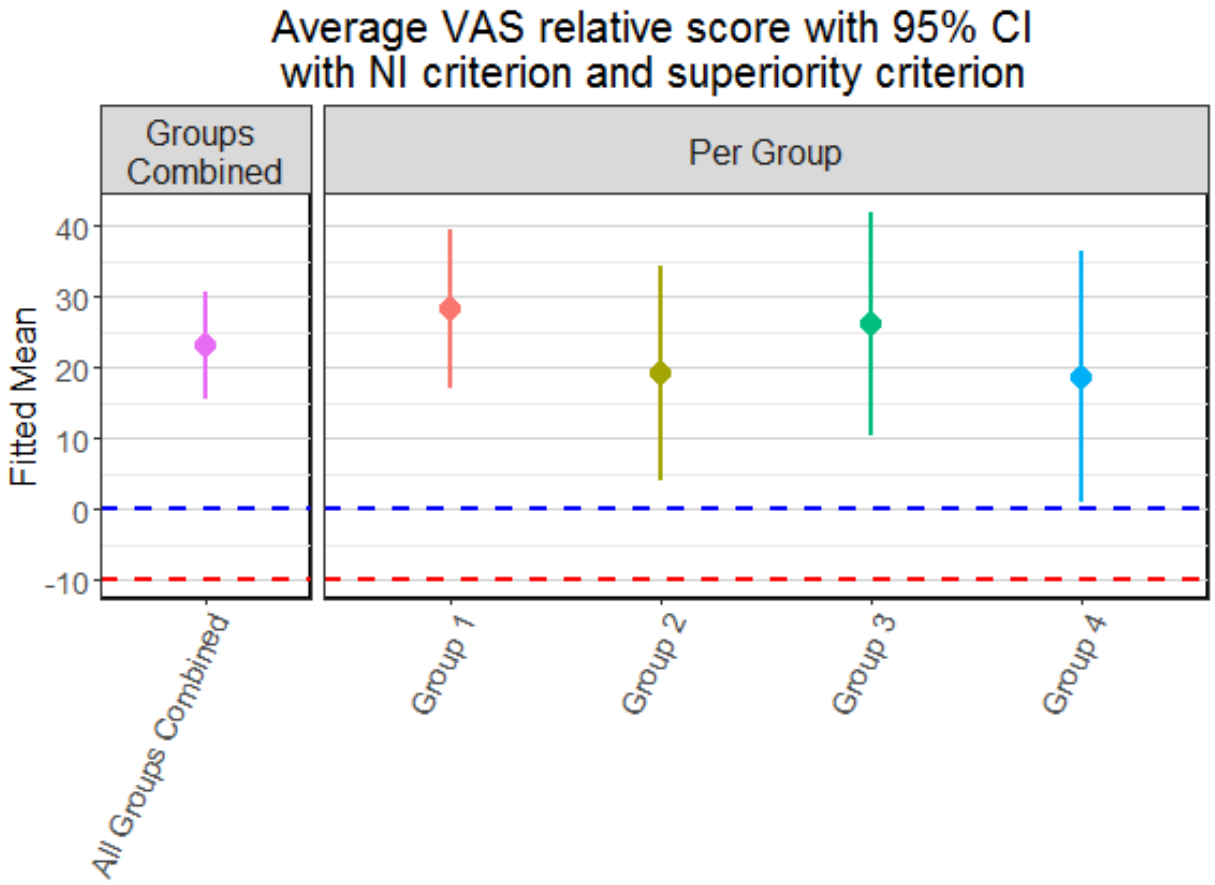

Figure 5: Average relative VAS scores with confidence interval per pen needle group and overall. If the entire confidence interval is above -10, non-inferiority is demonstrated with 95% confidence and if the entire confidence interval is positive, Superiority is demonstrated with 95% confidence.

11.2.2 Binary Responses from Diary (for Secondary Objectives)

All binary responses from the diaries will be summarized as in Table 5 and Figure 6. In addition, the percentage of subjects experiencing at least one of the binary event will be summarized per PN group and PN (cf. Table 6).

The difference in proportion of observed events with "Yes" recorded will be provided as in Table 7 for BD Nucleus vs. Current Pen needle.

Table 5: Percentage of Observed Bleeding events

Pen Needle Group	Pen Needle	Bleeding	95% CI
Group 1	Nucleus pen needle	65/2142 (3.0%)	(2.4%, 3.8%)
Group 1	Current 32G pen needle	90/1998 (4.5%)	(3.7%, 5.5%)
Group 2	Nucleus pen needle	43/857 (5.0%)	(3.8%, 6.7%)
Group 2	Current 32G pen needle	37/1020 (3.6%)	(2.6%, 5.0%)
Group 3	Nucleus pen needle	28/1023 (2.7%)	(1.9%, 3.9%)
Group 3	Current 32G pen needle	31/906 (3.4%)	(2.4%, 4.8%)
Group 4	Nucleus pen needle	39/636 (6.1%)	(4.5%, 8.3%)
Group 4	Current 32G pen needle	40/695 (5.8%)	(4.2%, 7.7%)

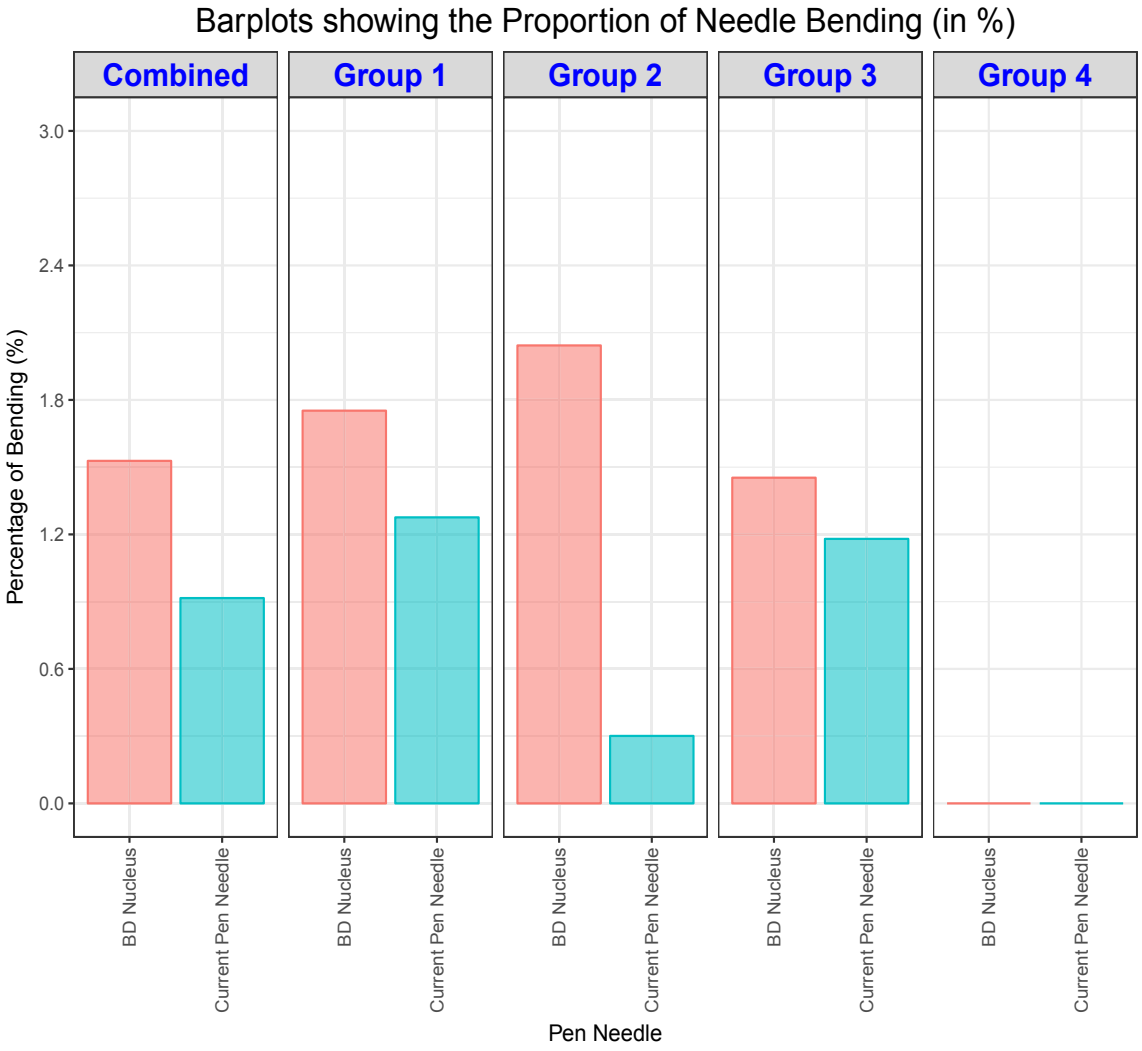

Figure 6: Barplots showing the Proportion of Needle Bruising

Table 6: Percentage of Subjects who experienced Bleeding or not

	FALSE	TRUE	Total
Group 1_Current 32G pen needle	35 (64.8%)	19 (35.2%)	54
Group 1_Nucleus pen needle	35 (59.3%)	24 (40.7%)	59
Group 2_Current 32G pen needle	19 (65.5%)	10 (34.5%)	29
Group 2_Nucleus pen needle	16 (59.3%)	11 (40.7%)	27
Group 3_Current 32G pen needle	16 (55.2%)	13 (44.8%)	29
Group 3_Nucleus pen needle	18 (60.0%)	12 (40.0%)	30
Group 4_Current 32G pen needle	12 (57.1%)	9 (42.9%)	21
Group 4_Nucleus pen needle	13 (54.2%)	11 (45.8%)	24

Table 7: Difference in Percentage of Bleeding occurrences. A negative difference indicates that the observed percentage with BD Nucleus is smaller than the observed percentage with Current/Assigned PN and a positive difference indicates that the observed percentage with BD Nucleus is larger than the observed percentage with Current/Assigned PN. If the upper limit of the 95% CI is less than the non-inferiority criterion of 4%, there is 95% confidence that BD Nucleus is non-inferior to the Current/Assigned PN.

Group	Comparison	Difference in Percentage of Bleeding	95% CI for Difference	PASS/FAIL 4%NI
Group 1	BD Nucleus PN vs Current/Assigned PN	-1.5%	(-2.7%, -0.3%)	PASS
Group 2	BD Nucleus PN vs Current/Assigned PN	1.4%	(-0.4%, 3.3%)	PASS
Group 3	BD Nucleus PN vs Current/Assigned PN	-0.7%	(-2.3%, 0.9%)	PASS
Group 4	BD Nucleus PN vs Current/Assigned PN	0.4%	(-2.2%, 3.0%)	PASS

11.2.3 Leakage from the Injection Site

The distribution of Leakage Scores per Pen Needle per subgroup will be provided as in Table 8 and Figure 7.

The leakage on a binary scale will also be presented and analyzed as in Section 11.2.2.

Table 8: Distribution of Leakage Score per Pen Needle per subgroup

Pen Needle	Score	Combined	Group 1	Group 2	Group 3	Group 4
BD Nucleus	0	62 (27.8 %)	18 (29 %)	5 (8.2 %)	9 (13.6 %)	12 (14.6 %)
	1	31 (13.9 %)	7 (11.3 %)	5 (8.2 %)	17 (25.8 %)	14 (17.1 %)
	2	43 (19.3 %)	5 (8.1 %)	12 (19.7 %)	14 (21.2 %)	7 (8.5 %)
	3	22 (9.9 %)	10 (16.1 %)	12 (19.7 %)	12 (18.2 %)	15 (18.3 %)
	4	47 (21.1 %)	9 (14.5 %)	18 (29.5 %)	5 (7.6 %)	20 (24.4 %)
	5	18 (8.1 %)	13 (21 %)	9 (14.8 %)	9 (13.6 %)	14 (17.1 %)
	Total	223	62	61	66	82
	All Score: >0	161 (72.2 %)	44 (71 %)	56 (91.8 %)	57 (86.4 %)	70 (85.4 %)
Current	0	85 (35.9 %)	20 (22.7 %)	7 (10.6 %)	6 (7.4 %)	14 (22.2 %)
	1	31 (13.1 %)	12 (13.6 %)	12 (18.2 %)	20 (24.7 %)	18 (28.6 %)
	2	39 (16.5 %)	16 (18.2 %)	6 (9.1 %)	8 (9.9 %)	8 (12.7 %)
	3	22 (9.3 %)	8 (9.1 %)	8 (12.1 %)	20 (24.7 %)	7 (11.1 %)
	4	44 (18.6 %)	19 (21.6 %)	18 (27.3 %)	7 (8.6 %)	5 (7.9 %)
	5	16 (6.8 %)	13 (14.8 %)	15 (22.7 %)	20 (24.7 %)	11 (17.5 %)
	Total	237	88	66	81	63
	All Score: >0	152 (64.1 %)	68 (77.3 %)	59 (89.4 %)	75 (92.6 %)	49 (77.8 %)

Figure 7: Barplots showing the Distribution of Leakage Score among the Injections per Pen Needle per subgroup

11.2.4 Exploratory Objectives

All binary responses will be summarized as in Section 11.2.2.

The difference in proportion of BD Nucleus vs. Current/Assigned Pen needle with a "Yes" response will be provided as in Table 7, but no criterion will be applied.

11.3 Additional Analysis

Analysis for the primary and secondary objectives will be performed on the intent-to-treat (ITT) population for information and presented in Appendix.

11.4 Demographics and Diabetes History

Table 9: Gender distribution - Randomized Subjects

Gender	Group 1	Group 2	Group 3	Group 4	Overall
Male	30 (52.63 %)	42 (70 %)	43 (74.14 %)	50 (84.75 %)	165 (70.51 %)
Female	27 (47.37 %)	18 (30 %)	15 (25.86 %)	9 (15.25 %)	69 (29.49 %)

Table 10: Distribution of Type of Diabetes - Randomized Subjects

Characteristics	Category	Group1	Group2	Group3	Group4	Overall
Diabetes	Type I	13 (50 %)	6 (42.86 %)	5 (26.32 %)	19 (65.52 %)	43 (48.86 %)
	Type II	13 (50 %)	8 (57.14 %)	14 (73.68 %)	10 (34.48 %)	45 (51.14 %)

Table 11: Diabetes History

Characteristics	Category	Group1	Group2	Group3	Group4	Overall
Frequency of Injection per day	Once	9 (21.95 %)	18 (21.95 %)	12 (22.22 %)	3 (5.66 %)	42 (18.26 %)
	Twice	5 (12.2 %)	16 (19.51 %)	9 (16.67 %)	13 (24.53 %)	43 (18.7 %)
	Three	6 (14.63 %)	16 (19.51 %)	20 (37.04 %)	19 (35.85 %)	61 (26.52 %)
	Four	13 (31.71 %)	18 (21.95 %)	5 (9.26 %)	14 (26.42 %)	50 (21.74 %)
	Five or more	8 (19.51 %)	14 (17.07 %)	8 (14.81 %)	4 (7.55 %)	34 (14.78 %)
Inject medications that are not insulin?	Yes	19 (50 %)	9 (40.91 %)	12 (75 %)	7 (58.33 %)	47 (53.41 %)
	No	19 (50 %)	13 (59.09 %)	4 (25 %)	5 (41.67 %)	41 (46.59 %)
Frequency of non-insulin diabetes pen	Per day	16 (51.61 %)	14 (70 %)	19 (59.38 %)	4 (50 %)	53 (58.24 %)
	Per week	13 (41.94 %)	3 (15 %)	12 (37.5 %)	3 (37.5 %)	31 (34.07 %)
	Not applicable	2 (6.45 %)	3 (15 %)	1 (3.12 %)	1 (12.5 %)	7 (7.69 %)
Same needle Type for both insulin and non-insulin pen?	Yes	13 (52 %)	11 (42.31 %)	3 (15 %)	18 (48.65 %)	45 (41.67 %)
	No	11 (44 %)	15 (57.69 %)	15 (75 %)	18 (48.65 %)	59 (54.63 %)
	Not applicable	1 (4 %)	0 (0 %)	2 (10 %)	1 (2.7 %)	4 (3.7 %)
Largest Amount of insulin in a single dose	1 - 20 units	11 (20.75 %)	18 (35.29 %)	9 (15.79 %)	4 (10.81 %)	42 (21.21 %)
	21 - 40 units	17 (32.08 %)	6 (11.76 %)	20 (35.09 %)	17 (45.95 %)	60 (30.3 %)
	41 - 60 units	18 (33.96 %)	9 (17.65 %)	11 (19.3 %)	13 (35.14 %)	51 (25.76 %)
	> 60 units	7 (13.21 %)	18 (35.29 %)	17 (29.82 %)	3 (8.11 %)	45 (22.73 %)
Total amount of insulin in a single day	1 - 40 units	7 (13.73 %)	18 (47.37 %)	7 (15.22 %)	17 (43.59 %)	49 (28.16 %)
	41 - 80 units	11 (21.57 %)	9 (23.68 %)	16 (34.78 %)	10 (25.64 %)	46 (26.44 %)
	81 - 120 units	20 (39.22 %)	8 (21.05 %)	11 (23.91 %)	9 (23.08 %)	48 (27.59 %)
	> 120 units	13 (25.49 %)	3 (7.89 %)	12 (26.09 %)	3 (7.69 %)	31 (17.82 %)
Most used injection site	Abdomen	7 (13.73 %)	4 (12.12 %)	13 (23.64 %)	16 (28.07 %)	40 (20.41 %)
	Arm	6 (11.76 %)	3 (9.09 %)	9 (16.36 %)	15 (26.32 %)	33 (16.84 %)
	Thigh	17 (33.33 %)	13 (39.39 %)	14 (25.45 %)	6 (10.53 %)	50 (25.51 %)
	Buttocks	6 (11.76 %)	5 (15.15 %)	15 (27.27 %)	3 (5.26 %)	29 (14.8 %)
	Other	15 (29.41 %)	8 (24.24 %)	4 (7.27 %)	17 (29.82 %)	44 (22.45 %)
Second most used injection site	Abdomen	4 (8.16 %)	8 (17.39 %)	16 (20.78 %)	3 (6 %)	31 (13.96 %)
	Arm	17 (34.69 %)	13 (28.26 %)	7 (9.09 %)	17 (34 %)	54 (24.32 %)
	Thigh	3 (6.12 %)	11 (23.91 %)	18 (23.38 %)	5 (10 %)	37 (16.67 %)
	Buttocks	15 (30.61 %)	9 (19.57 %)	16 (20.78 %)	12 (24 %)	52 (23.42 %)
	Other	10 (20.41 %)	5 (10.87 %)	20 (25.97 %)	13 (26 %)	48 (21.62 %)

Table 12: Demographic Categorical Characteristics

Characteristics	Category	Group1	Group2	Group3	Group4	Overall
Ethnicity	Hispanic / Latino	25 (54.35 %)	15 (65.22 %)	14 (43.75 %)	10 (41.67 %)	64 (51.2 %)
	Non Hispanic / Latino	21 (45.65 %)	8 (34.78 %)	18 (56.25 %)	14 (58.33 %)	61 (48.8 %)
Race	American Indian / Alaska Native	19 (19.19 %)	9 (8.49 %)	24 (22.43 %)	13 (12.75 %)	65 (15.7 %)
	Asian	11 (11.11 %)	13 (12.26 %)	10 (9.35 %)	9 (8.82 %)	43 (10.39 %)
	Black / African American	10 (10.1 %)	21 (19.81 %)	16 (14.95 %)	11 (10.78 %)	58 (14.01 %)
	Native Hawaiian / Pacific Islander	12 (12.12 %)	10 (9.43 %)	9 (8.41 %)	22 (21.57 %)	53 (12.8 %)
	White / Caucasian	19 (19.19 %)	17 (16.04 %)	11 (10.28 %)	18 (17.65 %)	65 (15.7 %)
	Subject refuse to disclose	9 (9.09 %)	18 (16.98 %)	23 (21.5 %)	23 (22.55 %)	73 (17.63 %)
	Other / Combination of two or more races	19 (19.19 %)	18 (16.98 %)	14 (13.08 %)	6 (5.88 %)	57 (13.77 %)
Country	China	10 (9.71 %)	0 (0 %)	1 (1.43 %)	6 (5.94 %)	17 (4.9 %)
	Vietnam	10 (9.71 %)	4 (5.48 %)	8 (11.43 %)	4 (3.96 %)	26 (7.49 %)
	Cambodia	10 (9.71 %)	1 (1.37 %)	0 (0 %)	8 (7.92 %)	19 (5.48 %)
	Japan	8 (7.77 %)	10 (13.7 %)	3 (4.29 %)	9 (8.91 %)	30 (8.65 %)
	Laos	3 (2.91 %)	3 (4.11 %)	4 (5.71 %)	10 (9.9 %)	20 (5.76 %)
	Korea	4 (3.88 %)	4 (5.48 %)	3 (4.29 %)	10 (9.9 %)	21 (6.05 %)
	Thailand	4 (3.88 %)	8 (10.96 %)	9 (12.86 %)	8 (7.92 %)	29 (8.36 %)
	Philippines	9 (8.74 %)	5 (6.85 %)	6 (8.57 %)	3 (2.97 %)	23 (6.63 %)
	Malaysia	7 (6.8 %)	8 (10.96 %)	3 (4.29 %)	1 (0.99 %)	19 (5.48 %)
	India	9 (8.74 %)	4 (5.48 %)	2 (2.86 %)	9 (8.91 %)	24 (6.92 %)
	Indonesia	9 (8.74 %)	6 (8.22 %)	9 (12.86 %)	9 (8.91 %)	33 (9.51 %)
	Other	20 (19.42 %)	20 (27.4 %)	22 (31.43 %)	24 (23.76 %)	86 (24.78 %)

Table 13: Demographic and Other Continuous Characteristics

Characteristics	Category	Group 1	Group 2	Group 3	Group 4	Overall
Age	N	44	41	45	38	168
	N Missing	0	1	2	0	3
	Mean	43	45	43	39	40
	Std. Dev.	5	3	4	4	4
	Mean CI (95 %)	21.67, 43.56	27.12, 51.27	28.35, 37.89	29.26, 49.28	25.78, 51.37
	Median	44	45	39	39	42
	Range	18, 55	20, 51	21, 45	29, 59	18, 59
How long ago were you diagnosed with diabetes? (in yrs.)	N	50	45	41	43	179
	N Missing	0	1	2	0	3
	Mean	3	2	3	2	5
	Std. Dev.	3	4	3	2	5
	Mean CI (95 %)	0.3, 7.2	0.21, 9.2	0.9, 6.6	0.17, 1.2	0.19, 1.3
	Median	15	6	6	7	3
	Range	0.1, 15	0.25, 17.1	0.29, 7.4	0.11, 6.8	0.1, 17.1
How long have you been injecting insulin? (in yrs.)	N	34	41	32	36	143
	N Missing	0	1	2	0	3
	Mean	1	9	2	11	9
	Std. Dev.	2	5	2	2	4
	Mean CI (95 %)	0.3, 7.2	0.21, 9.2	0.9, 6.6	0.17, 1.2	0.19, 1.3
	Median	5	5	7	11	11
	Range	0.1, 15	0.35, 16.1	0.29, 7.4	0.11, 6.8	0.1, 16.1

12 Appendix

12.1 Discontinued Data

The Table 14 shows the detailed list of discontinued subjects.

Table 14: Details of Discontinued Subjects

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

12.2 Missing Data

All the Missing data will be listed.

12.3 Adverse Events

Data listings will be provided for any adverse events and serious adverse event in Table 15. Adverse events will be summarized descriptively by pen needle and study group in Table 16 and 17.

Table 15: Data listing for adverse events

Random ID	Group	PN Used	Seriousness	Severity	Relation to product	Contribution of product malfunction	Relation to protocol	Description
R055	Group 1	BD Nano 32Gx4mm	Serious	Moderate	Related	Yes	Not related	adverse event to be described
R001	Group 4	Owen Mumford PenTips 32Gx4mm	Serious	Mild	Unlikely related	No	Possibly related	adverse event to be described
R099	Group 2	NovoTwist 32Gx5mm	Serious	Severe	Possibly related	Yes	related	adverse event to be described

Table 16: Summary of Adverse Events: Relationship to product

Group	Pen Needle	Number of events	Number of Subjects	Not related	Unlikely related	Possibly related	Related
Group 1	BD Nano 32Gx4mm	5	2	2	1	1	1
	BD Nucleus	0	0	0	0	0	0
Group 2	NovoFine Plus 32Gx4mm	0	0	0	0	0	0
	NovoTwist 32Gx5mm	0	0	0	0	0	0
	BD Nucleus	0	0	0	0	0	0
Group 3	NovoFine 32Gx6mm	0	0	0	0	0	0
	BD Nucleus	3	2	1	0	2	0
Group 4	Other	0	0	0	0	0	0
	BD Nucleus	0	0	0	0	0	0

Table 17: Summary of Adverse Events: Relationship to protocol / procedure

Group	Pen Needle	Number of events	Number of Subjects	Not related	Unlikely related	Possibly related	Related
Group 1	BD Nano 32Gx4mm	5	2	2	1	1	1
	BD Nucleus	0	0	0	0	0	0
Group 2	NovoFine Plus 32Gx4mm	0	0	0	0	0	0
	NovoTwist 32Gx5mm	3	3	0	1	0	2
	BD Nucleus	0	0	0	0	0	0
Group 3	NovoFine 32Gx6mm	0	0	0	0	0	0
	BD Nucleus	3	2	1	0	2	0
Group 4	Other	0	0	0	0	0	0
	BD Nucleus	0	0	0	0	0	0