Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04143945
Sponsor trial ID:	INS-4603
Official title of study:	A trial to compare the injection site pain experience of 0.25 mg semaglutide B and semaglutide D administered sc
Document date	26 August 2020

16.1.9 Documentation of Statistical Methods

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

Statistical Analysis Plan

Sponsor:	Novo Nordisk A/S
Protocol No:	INS-4603
Protocol Title:	A TRIAL TO COMPARE THE INJECTION SITE PAIN EXPERIENCE OF 0.25 MG SEMAGLUTIDE B AND SEMAGLUTIDE D ADMINISTERED SC
[redacted] **Project ID:**	[redacted]
Version Date:	10-Dec-2019 (SAP)

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	[redacted]
Signature of Sponsor Representative / Date:	
Name of Author / Title:	
Signature of Author / Date:	

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Novo Nordisk Protocol Version 2.0.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the SAP has been developed using the protocol dated 18-Oct-2019 (including all amendments up to this protocol date) and the final eCRF(s) dated 24-Oct-2019.

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the [redacted] Early Development Services (EDS) Biostatistics Department.

[redacted] EDS will evaluate the safety and tolerability analysis with focus on the injection site pain experience of two different pen-injectors.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in Section 9.8.2 of the CSR. Changes to planned analyses after unblinding do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

The primary objective is to compare, in healthy subjects, the injection site pain experience of a single dose of 0.25 mg semaglutide subcutaneously (sc), given as the DV3396 product, to that of the PDS290 product

5.1.1 Primary Endpoint

Endpoint Title	Time Frame	Unit
Intensity of injection site pain	1 min after each injection (Day 1)	Millimeter (mm) on a 100-mm horizontal visual-analogue scale [VAS] (where 0 mm= no pain, 100 mm = unbearable pain)

5.2 Exploratory

Comparison of injection site pain experience of the two products will be further explored by:

- Categorial assessments by means of a 6-point scale, and a derived dichotomous scale;
- Quality of pain;
- Duration of pain;
- Comparative pain experience by means of a 5-point scale, and a derived dichotomous scale;

5.2.1 Exploratory Endpoint

Endpoint Title	Time Frame	Unit
Categorical assessment of injection site pain intensity	Immediately after rating of intensity of injection site pain, ie, after 1 min plus the time it takes to complete the rating of intensity of injection site pain by visual analogue scale (Day 1)	6-point scale (none – very mild – mild – moderate – severe – very severe)
Moderate or more injection site pain	Dichotomous variable based on categorical assessment of intensity of injection site pain (Day 1) (item above)	Yes = moderate, severe, very severe No = none, very mild, mild
Quality of pain	Immediately after categorical assessment of intensity of injection site pain, ie, after 1 min plus the time it takes to complete the rating of intensity of injection site pain and the categorical rating of intensity of injection site pain (Day 1)	Pain quality items on short-form McGill Pain Questionnaire [modified SF-MPQ-2 inventory] (select all that apply): Throbbing pain ☐ Shooting pain ☐ Stabbing pain ☐ Sharp pain ☐ Cramping pain ☐ Gnawing pain ☐ Hot-burning pain ☐ Aching pain ☐ Heavy pain ☐ Tender ☐ Splitting pain ☐ Tiring-exhausting ☐ Sickening ☐ Fearful ☐ Punishing-cruel ☐ Electric-shock pain ☐ Cold-freezing pain ☐ Piercing ☐
Duration of pain	From time of injection until cessation of pain (Day 1)	min and sec
Comparative pain experience	After pain has ended after the last injection (Day 1)	5-point scale (the last injection hurt much more than the first injection – the last injection hurt more than the first injection – they hurt about the same

Endpoint Title	Time Frame	Unit
		[includes: none of the injections hurt] – the last injection hurt less than the first injection – the last injection hurt much less than the first injection)
The DV3396 product hurt less than or about the same as the PDS290 product	Dichotomous variable based on "Comparative pain experience" variable above (Day 1)	Yes = "about the same" (includes "none of the products hurt" or "the DV3396 product hurt less than the PDS290 product" or "the DV3396 product hurt much less than the PDS290 product") No = "The DV3396 product hurt much more than the PDS290 product" or "The DV3396 product hurt more than the PDS290 product"

5.3 Study Hypothesis

Not applicable.

6.0 Study Design

This is a single-center, cross-over, randomized, double-blind study in healthy men and women comparing the injection site pain experience of the DV3396 product to that of the PDS290 product when both products are used to deliver 0.25 mg semaglutide sc. A total of 104 subjects are planned to be randomized to achieve at least 100 completed subjects. The aim is to have an even distribution of males and females in the study; at least 30% of the same sex should be randomized in the study. Subjects will be randomized in a 2×2 scheme evenly to 4 sequences A,B,C or D of product and injection side as in Table 1.

Table 1 Product and site of injection on abdomen per treatment

Sequence	Sequence Description	Ratio Required
First injection on right side, Second injection on left side		
A	DV3396 (Right) followed by PDS290 (Left)	1
C	PDS290 (Right) followed by DV3396 (Left)	1
First injection on left side, Second injection on right side		
B	DV3396 (Left) followed by PDS290 (Right)	1
D	PDS290 (Left) followed by DV3396 (Right)	1

Subjects will receive 1 dose of semaglutide 0.25 mg with the DV3396 product and 1 dose of semaglutide 0.25 mg with the PDS290 product. The 2 products will be administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline. If pain experience still exists after 60 minutes, the second injection will not be administered. A follow-up phone call (last subject last visit) will take place between 4 and 5 weeks after drug administrations on Day 1.

6.1 Sample Size Considerations

The sample size calculation considers both the primary endpoint and the dichotomous endpoints.

With 100 subjects, a conservative standard deviation of 30 mm on the VAS, and 90% power, it is possible to detect a difference smaller than 10 mm. Hence a sample size of 100 subjects is considered sufficient to detect a clinically important difference. Allowing for 4% dropouts or missing data, a total of 104 subjects will need to be randomized.

Considering precision on the proportion of the dichotomous endpoints, a sample size of 100 subjects results in a confidence interval (CI) with a width of 10% on each side, e.g. for a proportion of 60%, the CI is 60% (50%-70%).

6.2 Randomization

Subjects who have met all eligibility criteria will receive a subject number upon inclusion in the study. They receive the subject number just prior to dosing. The subject number will ensure identification throughout the study. The subject number will be the same as the randomization number given on the randomization list provided by Novo Nordisk.

The randomization list will be transferred to the [redacted] Pharmacy and kept in a restricted area to which only the [redacted] Pharmacy has access.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

Additional statistical analyses will be performed on the exploratory endpoints. See Sections 16.1.1.2, 16.1.1.4, and 16.1.1.5 for more details on these analyses.

7.2 Interim Analysis and Key Results

A set of topline tables, figures and listings (TFLs) will be provided after Database (DB) lock-1 (without follow up data). The study will be unblinded after this DB lock-1. These TFLs are indicated with a * in Appendix 4: List of End of Text Outputs .

7.3 Final Analysis

All TFLs will be provided after DB lock-2 (all data included).

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the [redacted] Data Management Plan for the study. Two DB locks are planned:

DB lock-1 : includes all data except follow up data. These data will be used for topline TFLs.

DB lock-2 : includes all data. These data will be used for draft and final TFLs.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after each DB lock. Only quality assured (QA'd) results released by the Safety Laboratory will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be

sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all summaries, the mean, standard deviation (SD) and median will be presented to one decimal place greater than the data, and the minimum (min) and maximum (max) will be presented to the same number of decimal places as the data. Frequency percentages will be presented with one decimal.

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics.

P-values will be reported to four decimal places; p-value less than 0.0001 will be reported as p <0.0001.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, SD, min, median and max.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data the categories will be presented in the tables exactly as they appear in the CRF / Database, unless otherwise indicated. For injection pain experience categories, categories will be combined to create dichotomic categories in addition to the original scale.

9.1.4 Pooling

Not applicable.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping

Label	Grouping
Study Treatment	0.25 mg semaglutide D sc - DV3396 product 0.25 mg semaglutide B sc - PDS290 product
Treatment	DV3396, PDS290
Dose Level	0.25 mg

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation	Note
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1	

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the [redacted]EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets to be classified as critical or non-critical. As the primary objective is to compare the injection site pain experience, the datasets considered critical are subject level analysis data (ADSL), adverse events analysis data (ADAE), and questionnaire analysis data (ADQS) [containing all injection site pain experience data]. As these are related to the primary objectives these datasets will be double programmed per the QC Plan.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the [redacted] EDS – ICH E3 compliant – CSR Template. The layout of TFLs will be according to the [redacted] EDS standards.

No table shells will be provided. The TFLs will be provided in Adobe PDF format.

Format:

- Page size: A4
- Data in listings will be sorted by subject number and number of injection. Side and treatment (product) will be added to the listings.
- For presentation of the tables, please refer to the sections in this SAP.
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.
- The following headers and labels will be used in the TFLs:

Treatment:	Injection Number	Injection Site
○ DV3396	○ Inj. 1	○ Left
○ PDS290	○ Inj. 2	○ Right

10.0 Analysis Sets

Analyses	All Subjects	Safety Set	Full Analysis Set	Per Protocol Set
Disposition Summaries	✓			
Safety Assessments		✓		
Baseline Characteristics			✓	✓
Endpoint Analyses				✓

Both the full analysis set and the per protocol set will be used for summaries. All analyses will be based on the per protocol analysis set except if it is specifically stated otherwise. Since the safety set and the full analysis set are the same, only the safety set will be used for the safety summaries.

The analysis sets are established before DB hardlock-1.

10.1 Safety Set

All subjects who have received at least 1 injection of semaglutide (includes any skin contact with study product whether the injection was completed or not).

10.2 Full Analysis Set (FAS)

All randomized subjects who have received at least 1 injection of semaglutide (includes any skin contact with trial product whether the injection was completed or not). In exceptional cases, subjects from the FAS may be excluded. In such cases the exclusion will be justified and documented before DB hard lock.

10.3 Per-Protocol Set

All subjects who have received both injections of semaglutide and have completed both intensity of injection site pain assessments of the primary endpoint.

11.0 Subject Disposition

The number and percentage of subjects randomized, dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

Individual data on randomization, dosing and completion will be listed.

12.0 Protocol Deviations and Violations

Protocol deviations/violations are collected throughout the study. Protocol deviations for the analysis sets will be described in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Individual demographic data will be listed.

Subject demographics at screening will be summarized descriptively for all subjects. All data in this summary will be collected at screening and will include the subjects' age (in years), gender, race, ethnicity, weight (in kg), height (in cm), body mass index (BMI) [in kg/m^2].

Demographics will be summarized for the safety, FAS, and per protocol sets (if different from the safety set).

13.2 Medical History

Medical history (including coding according to Medical Dictionary for Regulatory Activities [MedDRA], version 22.0, will be listed.

13.3 Other Baseline Characteristics

Previous medications (i.e., any recorded medications that start and end before administration of the study drug) will be listed.

Previous injection experience as recalled by the subject to the best of their ability will be listed: product name, dose, type [vial/syringe, prefilled syringe, autoinjector, other], indication, frequency of use, injection site, chronological period used.

Previous medications and previous injection experience will be coded by using the World Health Organisation (WHO) Drug Dictionary Enhanced (DDE). The version described in the Coding Conventions will be used (version 2019MAR01 B3).

Non-compliance to inclusion or exclusion criteria (if any) will be listed.

14.0 Concomitant Medications

Concomitant medication will be listed including coding (WHO-DDE version 2019MAR01 B3).

Concomitant medications are defined as those taken by the patient at any time between the date of study drug administration and study completion/discontinuation. Medication with start date being partially or completely missing will be assumed to be concomitant if it cannot be definitively shown that the medication did not occur during treatment.

In addition, non-drug treatments will be listed.

15.0 Treatment Compliance and Exposure

Study drug administration data including location of the injection will be listed by subject.

16.0 Safety Analyses

16.1 Safety Variables

The following safety variables will be summarized:

- Injection site pain experience:
  - Intensity of injection site pain VAS
  - Categorical assessment of injection site pain intensity (6-point scale; dichotomous scale)
  - Quality of pain modified SF-MPQ-2 inventory;
  - Duration of pain assessment
  - Comparative pain assessment (5-point scale, dichotomous scale);
- Adverse Events (AEs)

The following safety variables will be listed:

- Vital Signs (supine systolic and diastolic blood pressure and pulse rate)
- Electrocardiograms (ECG) (if post dose assessments are deemed relevant by the investigator)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Fridericia's) Interval
- Clinical Laboratory Evaluations (if post dose assessments are deemed relevant by the investigator)
  - Clinical Chemistry
  - Hematology
  - Hormones
- Physical Examination (if post dose assessments are deemed relevant by the investigator)

16.1.1 Injection Site Pain Experience

Summaries will be presented for the full analysis set, and in addition for the per protocol set if the sets are different from each other.

16.1.1.1 Intensity of injection Site Pain – VAS

The pain score will be measured on a visual analogue scale, from 'no pain' (0 mm) to 'unbearable pain' (100 mm). VAS score will be listed by subject and injection number, side and treatment will be added to the listing.

The following descriptive statistics will be presented: number of subjects, arithmetic mean, SD, coefficient of variation (CV), median, min and max. The results will be summarized by treatment, by injection number, by side, by treatment and injection number, and by treatment and side.

Ping pong plots with individual VAS scores will be presented for each treatment sequence (i.e. by treatment and side).

In addition, the primary endpoint will be analyzed for the per protocol population by a fixed analysis of variance model with VAS score as the dependent variable, and product, injection side (right side, left side), injection number (first injection, second injection), and subject as fixed effects.

From the model, the difference in VAS score between the 2 products is estimated and presented with a 95% CI and a p-value.

Model in SAS:

```
PROC MIXED data=VAS;  /*for per protocol population*/
  class product inj_number inj_side subject;      /*inj_number: first or second injection*/
                                                  /*inj_side: left or right*/
  model VAS = product inj_number inj_side subject  /  ddfm=satterthwaite;
  lsmeans product/ diff cl;
RUN;
```

The interpretation of the difference in VAS pain scores will be supported and contextualized by the results of the analyses of the exploratory endpoints.

16.1.1.2 Intensity of Injection Site Pain – Categorial Assessments

Categorical assessment of injection site pain intensity

The categorial pain score will be measured by a 6-point scale in which the pain intensity is rated by the subjects as follows: none - very mild – mild - moderate – severe – very severe.

Individual results will be listed by subject and injection number, side and treatment will be added to the listing.

The results will be summarized descriptively, by counting the number (and percentage) of subjects in each category. Missing scores will be a separate category. The results will be summarized by treatment.

Moderate or more injection site pain

The 6-point scale will be dichotomized in two categories to evaluate the experience of 'moderate or more injection site pain'. The two categories are:

- No: none - very mild - mild
- Yes: moderate – severe – very severe.

The results will be summarized descriptively by counting the number (and percentage) of subjects in each category. Missing scores will be a separate category. The results will be summarized by treatment, by injection number, by side, by treatment and injection number, and by treatment and side.

In addition, a statistical analysis will be conducted using a McNemar mid-p test (Fagerland et al. 2013) with Bonett-Price hybrid score (Fagerland et al. 2014) 95% confidence intervals comparing the two products on the moderate or more pain score (No vs Yes).

Model in SAS:

```
PROC FREQ data=Pain score;
        tables DV3396* PDS290 / alpha=0.05;
    exact mcnem / midp ;
RUN;
```

16.1.1.3 Quality of Pain - Modified SF-MPQ-2 Inventory

The quality of pain will be assessed using the modified SF-MPQ-2 inventory.

Individual results will be listed by subject and injection number, side and treatment will be added to the listing.

The results will be summarized descriptively by counting the number (and percentage) of subjects for each description of pain quality. Missing scores will be a separate category. The results will be summarized by treatment.

16.1.1.4 Duration of Pain Assessment

The duration of pain as indicated by the subject will be recorded from time of injection until cessation of pain in seconds.

Individual results will be listed by subject and injection number, side and treatment will be added to the listing.

The results will be summarized with the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, median, min and max. The results will be summarized by treatment, by injection number, by side, by treatment and injection number, and by treatment and side.

In addition, the conditional duration of pain, given there is pain, will be analyzed for subjects in the per protocol set who has a non-missing and non-zero duration of pain on both injections, by a fixed analysis of variance model with duration of pain as the dependent variable, and product, injection side (right side, left side), injection number (first injection, second injection), and subject as fixed effects.

From the model, the difference in VAS score between the 2 products is estimated and presented with a 95% CI and a p-value.

Model in SAS:

```
PROC MIXED data=Duration of pain;  /*for per protocol population*/
  class product inj_number inj_side subject;       /*inj_number: first or second injection*/
                                                   /*inj_side: left or right*/
  model  duration = product inj_number inj_side subject  /  ddfm=satterthwaite;
  lsmeans product/ diff cl;
RUN;
```

16.1.1.5 Comparative Pain Assessment

Comparative pain experience

The comparative pain assessment is a 5-point scale in which the subjects will compare the pain between the first and second injection to preserve blinding. After unblinding the scoring will be translated into the following 5-point scale:

- The DV3396 product hurt much more than the PDS290 product.
- The DV3396 product hurt more than the PDS290 product.
- The DV3396 and PDS290 products hurt about the same (includes: none of the products hurt).
- The DV3396 product hurt less than the PDS290 product.
- The DV3396 product hurt much less than the PDS290 product.

Individual results will be listed by subject.

The results will be summarized descriptively by counting the number (and percentage) of subjects in each category. Missing scores will be a separate category.

The DV3396 product hurt less than or about the same as the PDS290 product

The 5-point scale will be translated in two categories to evaluate if the DV3396 product hurt less than or about the same as the PDS290 product. The two categories are:

- Yes: This includes “none of the products hurt” or “the DV3396 product hurt less than the PDS290 product” or “the DV3396 product hurt much less than the PDS290 product”.
- No: This includes “the DV3396 product hurt much more than the PDS290 product” or “the DV3396 product hurt more than the PDS290 product”.

The results will be summarized descriptively by counting the number (and percentage) of subjects in each category. Missing scores will be a separate category.

In addition, a statistical analysis will be conducted presenting the proportion with Clopper Pearson 95% confidence interval of “DV3396 product hurt less than or about the same as the PDS290 product”.

Model in SAS:

```
PROC FREQ data=comparative_pain;
  tables score / binomial(exact) alpha=.05;
RUN;
```

16.1.2 Adverse Events

A treatment-emergent AE (TEAE) is defined as an event that has onset date on or after the day of the first injection and no later than 28 days after the day of the last injection (both injections are scheduled on Day 1), or has onset date before the day of the first injection and increases in severity in the period up to 28 days after the last injection. If the time is missing for an AE on a dosing day, the AE will be categorized as TEAE.

In general, TEAEs will not be assigned to one of the products (PDS290 or DV3396) because time between dosing is 30-60 minutes. Local tolerability TEAEs will be categorized by product (PDS290 or DV3396), based on the location of the injection site which is indicated for these TEAEs.

AE summaries will include TEAEs only, one table will present all TEAEs (all TEAEs), and one table will present TEAEs related to local tolerability only (categorized by product).

A breakdown of the number of events and number and percentage of subjects reporting each AE, categorized by body system and preferred term coded according to the (MedDRA, version 22.0), will be presented for all local tolerability TEAEs, categorized by product (PDS290 or DV3396). Subjects will only be counted once within each body system or preferred term per product. A similar table will be provided for all TEAEs, subject will only be counted once within each body system or preferred term.

The summary tables will present the counts in descending order by system organ class and preferred term (within a system organ class) based on the number of subjects experiencing the event.

Additional tables for all TEAEs and for local tolerability TEAEs (number of events and number and percentage of subjects) by severity (mild/moderate/severe) will be provided.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed.

A listing of AEs leading to study discontinuation will be provided.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times.
- Missing AE severity or relationship will be classified as missing severity or missing relationship.
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment.

- Missing AE start date will be assumed to be after treatment for the determination of TEAE and on treatment for single treatment studies but will not be attributed to treatment in studies with multiple treatments.

16.1.3 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

16.1.4 Laboratory Data

Clinical laboratory data will be presented using Système International (SI) units (also used in the Study data tabulation model [SDTM] Controlled Terminology).

All laboratory data will be listed by subject and scheduled time. Normal ranges (with units corresponding to the reported SI units) will be used directly from the clinical laboratory and will be included in the listings. Clinical laboratory results outside the reference range will be flagged. In case the out of reference range values were considered clinically significant by the investigator, this will also be indicated in the listings as well as in the AE. Comments with regard to the laboratory test results will be shown in a separate listing.

A summary listing with all out-of-range values will also be provided.

16.1.5 Vital Signs

All vital signs measurements will be listed by subject and timepoint.

16.1.6 Electrocardiograms

All ECG measurements will be listed by subject and timepoint. The physician's interpretation and the specification of any abnormalities will be provided in a separate listing by subject and timepoint.

16.1.7 Other Observations Related to Safety

17.1.6.1 Physical Examination

Findings at screening and changes from screening (if applicable) for the physical examination will be listed.

17.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A TRIAL TO COMPARE THE INJECTION SITE PAIN EXPERIENCE OF 0.25 MG SEMAGLUTIDE B AND SEMAGLUTIDE D ADMINISTERED SC. Version 2.0, Final, 18 October 2019.

Clinical Data Interchange Standards Consortium, Inc. , Analysis Data Model (ADaM), Version 2.1, 2009.

Clinical Data Interchange Standards Consortium, Inc., Analysis Data Model (ADaM) Implementation Guide, Version 1.1, 2016

Fagerland MW, Lydersen S, Laake P. The McNemar test for binary matched-pairs data: mid-p and asymptotic are better than exact conditional. BMC Medical Research Methodology 2013; 13:91.

Fagerland MW, Lydersen S, Laake P. Recommended tests and confidence intervals for paired binomial proportions. Statistics in Medicine 2014; 33:2850–2875.

Appendix 1: Glossary of Abbreviations

ADaM	Analysis data model
ADAE	Subject level analysis dataset
ADSL	Adverse events analysis dataset
AE	Adverse event
ADQS	Questionnaires analysis dataset
BMI	Body mass index
CDISC	Clinical Data Interchange Standard Consortium
CSR	Clinical study report
CI	Confidence interval
CV	Coefficient of variation
DB	Database
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
FAS	Full analysis set
HBA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mm	millimeter
N	Number of observations
PDF	Portable Document Format
QA'd	Quality assured
QC'd	Quality controlled
SAE	Serious adverse event
SAP	Statistical analysis plan
sc	Subcutaneous(ly)
SD	Standard deviation
SDTM	Study data tabulation model

SI	Système International
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures and listings
VAS	Visual analogue scale
WHO-DDE	World Health Organization – Drug Dictionary Enhanced

Appendix 2: Schedule of Assessments

Visit	Screening	Pretreatment	Treatment	Follow-up Phone Call
Study Day	**Days -21 to -1**	**Day 1**		**Day 29 to Day 36**
		Predose	**Dosing and After**	
Ambulatory	X	X	X	X
Admission		X		
Discharge			X	
Informed Consent	X			
Medical History	X			
Previous Injection Experience[a]	X			
Demographics	X			
Hand out of subject ID card		X		
Physical Examination	X		X[b]	
Body Height, Body Weight and BMI Calculation	X			
Serology (HBsAg, anti-HCV, anti-HIV-1 and -2)	X			
Urine Drug and Alcohol Screen	X	X		
Urine Pregnancy Test (Females of Childbearing Potential Only)	X	X		X[c]
Clinical Laboratory[d]	X		X[d]	
HbA1c	X			
12-lead ECG[e]	X		X[e]	
Vital Signs[f]	X		X	
Eligibility Check	X	X[g]		
Randomization and Stratification[h]		X		
Study Drug Administration[h]			X	
Intensity of Injection Site Pain VAS[i]			X	
Categorical Assessment of Injection Site Pain Intensity[j]			X	
Quality of Pain Modified SF-MPQ-2 Inventory[k]			X	
Duration of Pain[l]			X	
Comparative Pain Assessment[m]			X	
Previous and Concomitant Medication	X	X	X	X
AE Monitoring	X	X	X	X
Technical Complaints[n]		X	X	

Drug Accountability			X	

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; HbA1c=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; SF-MPQ-2=short-form McGill Pain Questionnaire 2; VAS=visual-analogue scale

[a] Previous injection experience as recalled by the subject to the best of their ability: product used (name, dose, type [vial/syringe, prefilled syringe, autoinjector, other], indication, frequency of use, injection site, chronological period used).

[b] Physical examination: this will be a focused examination only done if deemed relevant by the Investigator.

[c] For the check on pregnancy at the follow-up phone call, female subjects of childbearing potential will be handed out a urine pregnancy test on Day 1. They will have to do the pregnancy test at the earliest in the morning of Day 29 and at the latest in the morning of the follow-up phone call.

[d] Clinical laboratory tests (including clinical chemistry and hematology): at screening (non-fasting).
The same tests may be done after the second study drug administration on Day 1 prior to discharge, if deemed relevant by the Investigator.

[e] 12-lead ECG: at screening.
12-lead ECG may be done after the second study drug administration on Day 1 prior to discharge, if deemed relevant by the Investigator.

[f] Vital signs (supine systolic and diastolic blood pressure, and pulse): at screening and after the second study drug administration on Day 1 prior to discharge.

[g] Eligibility check on Day 1 before dosing concerns the urine pregnancy test (female subjects of childbearing potential only), urine drug and alcohol screen, and concomitant medication only.

[h] Subjects will be randomized in a 2×2 scheme evenly to 4 sequences of product and injection side as in the table below:

Treatment Short Identifier	Treatment Long Identifier	Ratio Required
First injection on right side, Second injection on left side		
A	DV3396 (Right) followed by PDS290 (Left)	1
C	PDS290 (Right) followed by DV3396 (Left)	1
First injection on left side, Second injection on right side		
B	DV3396 (Left) followed by PDS290 (Right)	1
D	PDS290 (Left) followed by DV3396 (Right)	1

Subjects will receive 1 dose of semaglutide 0.25 mg with the DV3396 product and 1 dose of semaglutide 0.25 mg with the PDS290 product within the same day. The 2 products will be administered at least 30 minutes apart, in the anterior aspect of the abdominal wall on opposite sides of the midline.

[i] One minute after each injection, the VAS to rate the intensity of injection site pain will be administered.

[j] The categorical assessment of injection site pain intensity (6-point scale) will be started after the VAS to rate the intensity of injection site pain has been completed after each injection.

[k] The quality of pain modified SF-MPQ-2 inventory will be started after the categorical assessment of injection site pain intensity (6-point scale) has been completed after each injection.

[l] Subjects have to indicate after each injection when the pain, if any, is gone.

[m] The comparative pain assessment (5-point scale) comparing pain between the 2 injections will be completed after the last injection.

[n] All technical complaints that occur, from the time of receipt of the product at the site until the time of the last usage of the product, must be collected and reported to Novo Nordisk.

Appendix 3: List of In-Text Tables

List of In-Text Tables and Figures:		
Output	**Title**	**Analysis Set**
Table	Summary of Subject Disposition	All Subjects
Table	Summary of Demographics	Safety
Table	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Local Tolerability	Safety
Table	Summary of Treatment Emergent Adverse Events by Severity for Treatment Emergent Adverse Events - Local Tolerability	Safety
Table	Summary of Intensity of Injection Site Pain - VAS	Per Protocol
Figure	Ping-Pong Plots of Individual VAS scores by treatment sequence	Per Protocol
Table	Statistical Analysis on Injection Site Pain - VAS	Per Protocol
Table	Summary of Intensity of Injection Site Pain - Moderate or more injection site pain	Per Protocol
Table	Statistical Analysis on Intensity of Injection Site Pain - Moderate or more injection site pain	Per Protocol
Table	Summary of Quality of Pain - Modified SF-MPQ-2 Inventory	FAS
Table	Summary of Duration of Pain	Per Protocol
Table	Statistical Analysis on Duration of Pain	Per Protocol
Table	Summary of Comparative Pain - 5-Point Scale	FAS
Table	Summary of Comparative Pain - DV3396 product hurt less than or about the same as the PDS290 product	Per Protocol
Table	Statistical Analysis on Comparative Pain - DV3396 product hurt less than or about the same as the PDS290 product	Per Protocol

Appendix 4: List of End of Text Outputs

TFLs indicated with a * will be presented in Topline results.

List of End of Text Tables and Figures:		
Output	**Title**	**Population Set**
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Subject Disposition	All subjects
Table 14.1.2 *	Summary of Demographics	Safety Extended with FAS, Per Protocol if different from Safety
Table 14.1.3	Summary of Dosing	Safety
Section 14.2 – Pharmacokinetic Data - Not Applicable		
Section 14.3 – Safety Data		
Table 14.3.1.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – all TEAEs	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by Severity for Treatment Emergent Adverse Events – all TEAEs	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Local Tolerability	Safety
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by Severity for Treatment Emergent Adverse Events - Local Tolerability	Safety
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	All Subjects
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR	
Table 14.3.4	Listing of Abnormal Laboratory Values	Safety
Table 14.3.5 *	Summary of Intensity of Injection Site Pain - VAS	Per Protocol, FAS
Figure 14.3.6 *	Ping-Pong Plots of Individual VAS Scores by Treatment sequence	Per Protocol
Table 14.3.7 *	Statistical Analysis on Injection Site Pain - VAS	Per Protocol
Table 14.3.8 *	Summary of Intensity of Injection Site Pain - 6-Point Categorial Scale	Per Protocol, FAS
Table 14.3.9 *	Summary of Intensity of Injection Site Pain - Moderate or more injection site pain	Per Protocol, FAS
Table 14.3.10 *	Statistical Analysis on Intensity of Injection Site Pain - Moderate or more injection site pain	Per Protocol
Table 14.3.11 *	Summary of Quality of Pain - Modified SF-MPQ-2 Inventory	Per Protocol,

		FAS
Table 14.3.12*	Summary of Duration of Pain	Per Protocol, FAS
Table 14.3.13 *	Statistical Analysis on Duration of Pain	Per Protocol
Table 14.3.14 *	Summary of Comparative Pain - 5-Point Scale	Per Protocol, FAS
Table 14.3.15 *	Summary of Comparative Pain - DV3396 product hurt less than or about the same as the PDS290 product	Per Protocol, FAS
Table 14.3.16 *	Statistical Analysis on Comparative Pain - DV3396 product hurt less than or about the same as the PDS290 product	Per Protocol

For the Topline results, additional plots might be created to support visualization of pain scores and /or consistency between the results on the different pain scales.

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 Disposition	
Listing 16.2.1.1	Subject Disposition
Listing 16.2.1.2	Deviation from Eligibility Criteria
Section 16.2.2 Protocol Deviations	
Listing 16.2.2.1	Reference to CSR
Section 16.2.3 Allocation to Analysis Sets	
Listing 16.2.3.1 *	Overview Analysis Sets
Section 16.2.4 Demographics Data and Other Baseline Characteristics	
Listing 16.2.4.1 *	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Previous Medications and Previous Injection Experience
Section 16.2.5 Compliance and/or Drug Concentration Data	
Listing 16.2.5.1	Study Dates
Listing 16.2.5.2 *	Study Drug Administration
Section 16.2.6 Injection Pain Experience Data	
Listing 16.2.6.1 *	Intensity of Injection Site Pain – VAS
Listing 16.2.6.2 *	Intensity of Injection Site Pain – Categorial Scale
Listing 16.2.6.3 *	Quality of Pain - Modified SF-MPQ-2 Inventory
Listing 16.2.6.4 *	Duration of Pain
Listing 16.2.6.5 *	Comparative Pain Assessment
Section 16.2.7 Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Study Drug Discontinuation
Listing 16.2.7.3	Concomitant Medications and Non Drug Therapies
Section 16.2.8 Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry
Listing 16.2.8.2	Clinical Laboratory Results – Hematology
Listing 16.2.8.3	Clinical Laboratory Results – Comments
Section 16.2.9 Other Safety Data	
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	12-Lead Electrocardiogram Results – Individual Parameters
Listing 16.2.9.3	12-Lead Electrocardiogram Results – Investigator's Interpretation and

	Specification of ECG Abnormalities
Listing 16.2.9.4	Physical Examination Findings

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.7	Randomization
Appendix 16.1.9.2	Statistical Appendices

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
02-Dec-2019	[redacted]	Draft for internal review
05-Dec-2019		First Draft to Novo Nordisk
10-Dec-2019		Final

STATISTICAL METHODS AND ANALYSIS OUTPUT

A TRIAL TO COMPARE THE INJECTION SITE PAIN EXPERIENCE OF 0.25 MG SEMAGLUTIDE B AND SEMAGLUTIDE D ADMINISTERED SC

CONFIDENTIAL

[redacted]code: [redacted]
Sponsor code: INS-4603

SPONSOR Novo Nordisk A/S

AUTHOR [redacted]MSc, Biostatistician

TABLE OF CONTENTS

1. Deviations from the SAP

None.

2. Analysis Populations

All 104 subjects were in the safety set, full analysis set and in the per protocol set.

3. Statistical Analysis Output

3.1 Statistical Analysis VAS

```
analysis primary VAS - fix: trtp aperiod side - ran: subject

The Mixed Procedure

          Number of Observations

Number of Observations Read             208
Number of Observations Used             208
Number of Observations Not Used           0


Covariance Parameter
      Estimates

Cov Parm     Estimate

Residual      80.5244


        Type 3 Tests of Fixed Effects

              Num     Den
Effect         DF      DF    F Value    Pr > F

TRTA            1     101       4.35    0.0395
APERIOD         1     101       7.74    0.0065
EXLAT           1     101       0.01    0.9386
SUBJID        103     101       2.09    0.0001


                                          Estimates

                         Standard
Label           Estimate Error      DF    t Value    Pr > |t|     Alpha   Lower    Upper

DV3396 - PDS290   2.5962 1.2444     101       2.09      0.0395      0.05  0.1276   5.0647


                                    Least Squares Means

           Actual                                          Standard
Effect     Treatment    Laterality Period    Estimate      Error      DF    t Value    Pr > |t|

TRTA       DV3396                             8.2788     0.8799     101       9.41      <.0001
TRTA       PDS290                             5.6827     0.8799     101       6.46      <.0001
APERIOD                           1           5.2500     0.8799     101       5.97      <.0001
APERIOD                           2           8.7115     0.8799     101       9.90      <.0001
EXLAT                 LEFT                   7.0288     0.8799     101       7.99      <.0001
EXLAT                 RIGHT                  6.9327     0.8799     101       7.88      <.0001
```

Statistical Analysis on Injection Site Pain - VAS

Per Protocol Set

Treatment Comparison (Test vs. Reference)	Parameter	LSmeans Test	LSmeans Reference	Difference Test/Reference Estimate	95% CI Lower	95% CI Upper	p value product
DV3396 - PDS290	VAS (mm)	8.28	5.68	2.6	0.1	5.1	0.0395

Model: ANOVA with a fixed effect for product (DV33 and PDS290), injection number (1st 2nd), injection side (left and right), and subject.

3.2 Statistical Analysis Duration of Pain

analysis Conditional Duration Pain - fix: trtp aperiod side - ran: subject

The Mixed Procedure

Number of Observations

Number of Observations Read	90
Number of Observations Used	90
Number of Observations Not Used	0

Covariance Parameter Estimates

Cov Parm	Estimate
Residual	213.59

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTA	1	42	0.87	0.3553
APERIOD	1	42	1.58	0.2162
EXLAT	1	42	2.85	0.0985
SUBJID	44	42	7.47	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
DV3396 - PDS290	3.0168	3.2277	42	0.93	0.3553	0.05	-3.4970	9.5305

Least Squares Means

Effect	Actual Treatment	Laterality	Period	Estimate	Standard Error	DF	t Value	Pr > |t|
TRTA	DV3396			26.1084	2.2311	42	11.70	<.0001
TRTA	PDS290			23.0916	2.2311	42	10.35	<.0001
APERIOD			1	22.5777	2.2288	42	10.13	<.0001
APERIOD			2	26.6223	2.2288	42	11.94	<.0001
EXLAT		LEFT		21.9890	2.1821	42	10.08	<.0001
EXLAT		RIGHT		27.2110	2.1821	42	12.47	<.0001

Table XXX Statistical Analysis on Duration of Pain

Per Protocol Set (conditional dataset)

Treatment Comparison (Test vs. Reference) product	Parameter	LSmeans Test	LSmeans Reference	Difference Test/Reference Estimate	95% CI Lower	95% CI Upper	p value
DV3396 - PDS290	Pain Duration (sec)	26.1	23.1	3.0	-3.5	9.5	0.3553

Model: ANOVA with a fed effect for product (DV3396 and PDS290), injection number (1st 2nd), injection side (left and right), and subject.
Note: The conditional duration of pain, given there is pain, is analyzed for subjects in the per protocol set who have a non-missing and non-zero duration of pain on both injections.

3.3 Statistical Analysis on Intensity of Injection Pain - Moderate or more injection site pain

analysis moderate or more injection site pain
McNemar paired exact mid-p test

The FREQ Procedure

Table of _11 by _22

_11(DV3396) _22(PDS290)

Frequency, Percent, Row Pct, Col Pct	Yes	No	Total
Yes	1	7	8
	0.96	6.73	7.69
	12.50	87.50	
	50.00	6.86	
No	1	95	96
	0.96	91.35	92.31
	1.04	98.96	
	50.00	93.14	
Total	2	102	104
	1.92	98.08	100.00

Statistics for Table of _11 by _22
McNemar's Test

Chi-Square	DF	Pr > ChiSq	Exact Pr >= ChiSq	Exact Mid p-Value
4.5000	1	0.0339	0.0703	0.0391

Simple Kappa Coefficient

Estimate	Standard Error	95% Confidence Limits	
0.1746	0.1668	-0.1524	0.5016

Sample Size = 104
_analysis moderate or more injection site pain
relative risk

The FREQ Procedure

Table of TRTA by AVALCAT1

TRTA(Actual Treatment)
AVALCAT1(Analysis Value Category 1)
Frequency,
Percent ,
Row Pct ,
Col Pct ,

	No	Yes	Total
DV3396	96	8	104
	46.15	3.85	50.00
	92.31	7.69	
	48.48	80.00	
PDS290	102	2	104
	49.04	0.96	50.00
	98.08	1.92	
	51.52	20.00	
Total	198	10	208
	95.19	4.81	100.00

Statistics for Table of TRTA by AVALCAT1

Odds Ratio and Relative Risks

Statistic	Value	95% Confidence Limits	
Odds Ratio	0.2353	0.0487	1.1359
Relative Risk (Column 1)	0.9412	0.8849	1.0010
Relative Risk (Column 2)	4.0000	0.8701	18.3891

Sample Size = 208

Table Statistical Analysis on Intensity of Injection Pain - Moderate or more injection site pain

Study Population: per protocol

Moderate or more Pain

Crosstabulation of categories for DV3396 (rows) versus PDS290 (cols)

	Yes	No
Yes	1	7
No	1	95

McNemar mid-p test and relative ratio with Bonett-Price hybrid score 95% CI

McNemar mid-p value	0.0391	
Ratio and 95% CI *	4.00	1.08 - 14.8

*: Relative incidence ratio of moderate or more pain for DV3396 over DPS290
No: none - very mild - mild Yes: moderate - severe - very severe.

3.4 Statistical Analysis on Comparative Pain - DV3396 versus PDS290

analysis proportion DV3396 hurt less/same as PDS290 with Clopper Pearson 95% CI

The FREQ Procedure

Analysis Value Category 1

AVALCAT1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Yes	65	62.50	65	62.50
No	39	37.50	104	100.00

Binomial Proportion
AVALCAT1 = Yes

Proportion	0.6250
ASE	0.0475

Confidence Limits for the Binomial Proportion
Proportion = 0.6250

Type	95% Confidence Limits	
Clopper-Pearson (Exact)	0.5247	0.7180

Test of H0: Proportion = 0.5

ASE under H0	0.0490
Z	2.5495
One-sided Pr > Z	0.0054
Two-sided Pr > |Z|	0.0108

Sample Size = 104

Table Statistical Analysis on Comparative Pain - DV3396 versus PDS290

Per Protocol Set

DV3396 hurts less/same as PDS290 *					
Yes		No		Proportion #	
n	(%)	n	(%)	Yes	95% CI
65	(62.5)	39	(37.5)	0.63	0.52 - 0.72

*: DV3396 product hurt less than or about the same as the PDS290 product.
#: Proportion "Yes" and Clopper-Pearson (Exact) 95% CI.