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STATISTICAL ANALYSIS PLAN

[PROTOCOL TITLE: A DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, PROOF-OF-CONCEPT STUDY IN SUBJECTS WITH ABDOMINAL OR THORACIC CHRONIC SCAR PAIN TO ASSESS THE ANALGESIC PROPERTIES OF INTRADERMAL DOSES OF DYSPORT®]

[D-FR-52120-244]

This statistical analysis plan is based on:
PROTOCOL VERSION AND DATE: 3.0 – 04 DECEMBER 2018

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APPROVAL PAGE

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The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

Name	Company	Function	Date	Signature
PPD	IPSEN	PPD	EA	EA
PPD	BIOTRIAL	PPD	EA	EA
PPD	IPSEN	PPD	EA	EA
PPD	IPSEN	PPD	EA	EA

EA: Electronic Approval

HISTORY OF CHANGES

Version Number	Date	Description/Rational for change

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Class
AUE	Area Under the Effect
C	Concomitant
CHMP	Committee for Medicinal Products for Human Use
CHG	Change from Baseline
CRF	Case Report Form
CSR	Clinical Study Report
E	Electronic
EA	Electronic Approval
ECG	Electrocardiogram
ED	Early Discontinuation
EMA	European Medicines Agency
EoS	End of Study
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
LOQ	Limit Of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
P	Prior
PC	Prior and Concomitant
PCSA	Potentially Clinically Significant Abnormalities
PN	Preferred Name
PP	Per Protocol
PPT	Pressure Pain Threshold
PT	Preferred Term
QoL	Quality of Life
QST	Quantitative Sensory Testing
SAE	Serious Adverse Event

ABBREVIATION	Wording Definition
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	Standard International
SMQ	Standardised MedDRA Query
SOC	System Organic Class
SOP	Standard Operating Procedure
SPID	Sum Pain Intensity Differences
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
U	Unit
WHO-DD	World Health Organization – Drug dictionary
WOCF	Worst Observation Carried Forward

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-FR-52120-244. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarized and analyzed, including specificities of the statistical analyses to be performed.
Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.
The SAP is to be finalized prior to database lock. A separate shell will be provided for tables, figures and listings.
Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per ICH E3).

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

The primary objective is:

- To describe the pharmacodynamic analgesic profile (time of onset of meaningful analgesic effect, peak-effect, time to peak-effect, duration of effect) of intradermal doses of Dysport in subjects with abdominal or thoracic chronic scar pain.

The secondary objectives are:

- To compare the efficacy of intradermal doses of Dysport to placebo.
- To assess the safety and tolerability of a range of intradermal doses of Dysport.

The exploratory objectives are:

- To explore improvement of quality of life (QoL) using SF-36 questionnaire.
- To explore concomitant use of rescue medication (analgesia).

2.2 Overall Study Design and Investigational Plan

The study will consist of two sequential parts, the first being to identify subjects who will potentially benefit from intradermal Dysport injection, 'responders', who will then progress to the second part, which is the double-blind study of the intradermal injection of Dysport or placebo:

- Part A: A double-blind, randomised, initial two-period cross-over run-in part, extended screening period of placebo or local anaesthetic (lidocaine),
- Part B: A single-dose, double-blind, randomised, parallel part with one of the three different doses of Dysport or placebo.

To ensure subjects will potentially benefit from intradermal injection of Dysport, they will be tested for responsiveness to local anaesthetic (lidocaine).

Study design is presented in details in section 3.1 of the protocol.

2.3 Sample Size Determination and Power

No prospective calculations of statistical power are made.
This is an exploratory trial which will use a standard early phase dosing scheme for single escalating dose and will also generate data for future regulatory trials.
An appropriate sample size cannot be determined statistically as no previous human data from previous clinical trials are available. A sample size of six subjects per dose of Dysport has been selected. Approximately 24 subjects (3 actives and 1 placebo per group so 4x6 subjects) will be randomised in the double-blind period. Subjects who withdraw within the six first weeks from dosing will be replaced.

2.4 Randomisation and Blinding (if applicable)

2.4.1 Pre-randomisation Run-in Period (Part A)

Following confirmation of eligibility after the screening visit, subjects will be assigned to a pre-randomisation run-in number and allocated to one of the two treatment sequence groups in a chronological order, i.e. first eligible subject after the screening visit will be given the first run-in number. Subjects will be randomised with a ratio 2:2 (blocks of eight subjects) to receive:

- Either lidocaine on injection test 1 then placebo (saline) on injection test 2,
- Or placebo (saline) on injection test 1 then lidocaine on injection test 2.

2.4.2 Randomised Double-Blind Period (Part B)

Subjects will be randomised to receive Dysport 2.5 U, Dysport 2.5 U placebo, Dysport 10 U, Dysport 10 U placebo, Dysport 20 U, Dysport 20 U placebo with a ratio 3:1:3:1:3:1 (blocks of 12 subjects).
Following confirmation of eligibility after injection test 2, subjects will be assigned to a randomisation number and allocated to one of the treatment groups in a chronological order, i.e. first eligible subject will be given the first randomisation number.

Mirror lists of randomisation numbers will also be produced to allow the randomisation of replacement subjects (e.g. the subjects who withdraw within six first weeks after Investigational Medicinal Product (IMP) dosing) or to be used for the replacement of kits which could be damaged during the IMP reconstitution. For example, number CCI will be used to randomise the replacement for the subject who was randomised with number CCI.

2.5 Schedule of Assessments

Schedule of assessments is presented in section 18.1 from the protocol.

2.6 Change from Statistical Section of the Protocol

The following endpoints were not planned in the statistical section of the Protocol but were added in section 5.7.4.1 (Efficacy parameters) and 5.7.5.1 (Rescue medication): SPID and AUE. The reason for this change is to have additional information for the description of the pain response. Date of agreement of change is 03MAY2019.
The sensitivity analyses originally planned in the protocol in section 11.3.3.2 to take into account the intake of rescue medication and to handle missing data will not be

performed due to the low number of rescue medication taken and the difficulty to associate the NRS score assessment to the rescue medication. This will be confirmed during the blind data review meeting, before the database lock. Date of agreement of change is 04JUN2019.

3 PLANNED ANALYSES

3.1 Safety Monitoring

No independent Data Monitoring Committee will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed.

3.3 Final Analysis

Planned analyses will be done when all subjects completed study and after database lock.

4 ANALYSIS POPULATIONS

4.1 Screened population

All subjects screened (i.e. who signed the informed consent).

4.2 Run-in population

All subjects who received at least one injection in the pre-randomisation run-in period (Part A).
For analyses and displays, subjects will be classified according to randomised treatment allocated in part A.

4.3 Randomised population

All subjects randomised in the double-blind period (Part B).

For analyses and displays, subjects will be classified according to randomised treatment allocated in part B.

4.4 Safety population

All subjects who received at least one dose of the study drug during the randomised double-blind period (Part B).
For analyses on the safety population, subjects will be classified according to treatment received. If there is any doubt whether a subject was treated or not, he/she will be assumed treated for the purposes of analysis.

4.5 Per Protocol (PP) Population

All subjects from the randomised population for whom no major protocol deviation occurred.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 8.
The statistical analyses will be performed by the Biostatistics unit of BIOTRIAL BIOMETRICS in agreement with the sponsor.

5.1 General Considerations

All statistical analyses will be performed using the SAS® software version 9.4 or higher.

For Part A, only listings will be provided. For Part B, tables, figures and listings will be provided.

5.1.1 Outputs Presentation

5.1.1.1 Tables Header

Depending on the type of data, the summary tables will be presented as follows:
- For disposition, demographic data and baseline data description: by treatment group and overall,
- For efficacy and safety data: by treatment group and all Dysport.

5.1.1.2 Presentation of Treatment Group

For Part A, listings will be displayed using the following treatment group labels, in the order presented:

Long label	Short label
Lidocaine 2.5mg/injection site	Lidocaine
Placebo	Pbo

For Part B, Tables, Figures and Listings (TFLs) will be displayed using the following treatment group labels, in the order presented:

Long label	Short label
Placebo	Pbo
Dysport 2.5U/Injection site	Dysport 2.5U*
Dysport 10U/Injection site	Dysport 10U*
Dysport 20U/Injection site	Dysport 20U*

* Per injection site

When specified, tables will also be described by total dose received in the painful injection area and the total dose received in the painful area divided by the painful area.

5.1.1.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using visit number as collected in the electronic Case Report Form (eCRF).
Visits in the TFLs will be presented as follows and in that order:

Part	Long Visit Name	Short Name
	Screening	Scr
Part A	Injection test 1 (Day -21 max)	Inj1
	Injection test 2 (Day -14 max)	Inj2
Part B	Baseline (Day -7 Day -1)	Bsl
	Day 1 Pre-dose	D1 Pre-dose
	Day 1 Post-dose	D1 Post-dose
	Day 2 Day 7	D2 D7
	Week 2	W2
	Week 4	W4
	Week 6	W6
	Week 8	W8
	Week 10	W10
	Week 12	W12
	Week 14	W14
	End of Study	EOS

5.1.2 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category. The missing category will be presented if there is one missing category for at least one treatment group. Except otherwise specified, subjects with missing data will not be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (SD), first quartile, median, third quartile, minimum and maximum. Missing data will be displayed.

5.1.3 Baseline value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken within 7 days prior to IMP administration (including unscheduled assessments).

For the spontaneous NRS score, baseline will be defined as the mean of all pre-dose data (from day -7 and including pre-dose on Day 1).

5.1.4 Reference Start Date and Study Day

Reference start date is defined as the day of IMP administration in Part B.
The day of IMP administration will be Day 1. Study day will be calculated as:
- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.
- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any Part B listings where an assessment date or event date appears.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the imputations described in appendix A3.

5.2 Randomisation, Disposition and Population

A listing presenting randomisation details will be provided for Part A and Part B separately.

Following disposition summaries and listings will be provided:

- Summary table with the number and percentage of subjects screened, screen failed, reason for screen failures, randomised, completers, withdrawn and reason for withdrawal, by treatment group and overall,
- Summary table on duration of subject participation in the study, for Part B. The definition of the duration of subject participation is from the date of consent to the last study visit,
- Summary table with the number and percentage of non-responders' subjects at the end of Part A,
- Listing of subject disposition,
- Listing of dates of visit including duration of subject participation,
- Listing of screen failure subjects with the criteria not met,
- Listing of withdrawal subjects,

Following analysis population summaries and listings will be provided:

- Listing of all inclusion criteria,
- Listing of subjects violated inclusion criteria,
- Listing of all exclusion criteria,
- Listing of subjects fulfilled exclusion criteria,
- Summary of the number and percentage of subjects in each analysis population by treatment group and overall, based on all randomised subjects with reasons for exclusion from each analysis population,
- Summary of the number and percentage of subjects in the run-in population with reasons for exclusion from this population,
- Listing including flag for each analysis population and reason for exclusion from each population.

5.3 Protocol Deviations

An exhaustive list of major protocol deviations that may occur during the study and any action to be taken regarding exclusion of subjects will be defined in Protocol Deviation Plan. Major protocol deviations will be determined before unblinding of the study, finalized during the blind data review and documented in a separate document.

Number and percentage of subjects with protocol deviations by deviation category (see DV section of Standard SDTM+ user guide) will be summarized on all randomised subjects. Listings of major protocol deviations will also be provided on the randomised population for Part B and on the run-in population for Part A.

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries will be provided for the randomised population. No statistical comparison between treatment groups will be performed.

Following summaries will be provided on:
- Demographic variables (refer to appendix A6 for EudraCT age categories),
- Other baseline characteristics (e.g. drug abuse tests, postmenopausal status, serology),
- Disease characteristics at day 1 pre-dose (e. g. longitudinal axis, total painful area and baseline values for spontaneous current pain NRS score),

Details of the surgery which caused the painful scar will be listed (Surgical procedure, indication and date of surgery).

Listings will also be provided for all the summaries listed above.
An additional listing with demographic variables for subjects non included in part B will also be provided.

5.5 Medical history, non-drug therapies, medications and surgical procedures

Medical and surgical history, non-drug therapies and surgical procedures will be coded using the latest version of MedDRA in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of WHO-Drug dictionary in effect within IPSEN at the time of database lock.

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the IMP administration (Part B) to allow classification as either Prior only, Prior and Concomitant, or Concomitant only:

Prior (P)	Start and stop dates prior to the date of IMP administration.
Prior and Concomitant (PC)	Start date before the date of IMP administration and stop date on or after the date of IMP administration.
Concomitant (C)	Start date on or after the date of IMP administration.

Summary tables on prior medications/non-drug therapies/surgical procedures will include “P” only, summary tables on concomitant medications/non-drug therapies/surgical procedures will include “C” and “PC”.

See detailed rules in appendix A3 for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date.

The therapeutic class will correspond to the second level of ATC code, that is, corresponding to the first 3 figures.

Following summaries, presenting count and percentages of subjects will be provided:

- Medical and surgical history by primary system organ class (SOC) and preferred term (PT),
- Prior medications (P) by ATC class and PN (ATC level 2),
- Concomitant medications (PC, C) by ATC class and PN (ATC level 2),
- Concomitant medications (PC, C) related to medical history by ATC class and PN (ATC level 2),
- Prior non-drug therapies (P) by primary SOC and PT,
- Concomitant non-drug therapies (PC, C) by primary SOC and PT,
- Concomitant surgical procedures (C) by primary SOC and PT,

A specific listing of medications from the class ANALGESICS, ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC. and PSYCHOANALEPTICS (ATC level 2) and a specific listing of the concomitant medication related to medical history will be provided.

Listings will be provided for all the summaries listed above for Part B. These listings should include a flag indicating the category (P, PC, C) as described in the table above.

5.6 Compliance

Treatment compliance will be summarized on the run-in population for Part A and on the safety population for Part B using a listing of administrations and planned and performed injected volumes (overall and by injection site).

5.7 Pharmacodynamic/Efficacy Part B

5.7.1 General Considerations

5.7.1.1 Significance Testing and Estimations

The statistical analysis of efficacy and safety is only descriptive therefore no formal statistical significance testing will be performed.

5.7.1.2 Statistical/analytical issues

Adjustments for Covariates
Not applicable

Handling of Dropouts or Missing Data
The strategy for missing data handling is specified in each relevant section.

Interim Analyses and Data Monitoring
Please refer to section 3.

Multicentre Studies
Not applicable

Multiple Comparisons/Multiplicity
No formal statistical significance testing will be performed.

Use of an "Efficacy Subset" of Subjects
Not applicable

Active-Control Studies Intended to Show Equivalence (if applicable)
Not applicable

Examination of Subgroups
Subgroups analyses will be detailed in the concerned sections.

5.7.2 Pre-randomisation run-in period

A listing presenting NRS data will be provided. The listing will present, by subject, the planned visit and timepoint, the treatment administered, the assessment dates and the NRS scores.

5.7.3 Randomised double-blind period: Analysis of Primary Efficacy Endpoint

5.7.3.1 Endpoint, Treatment Effect and Estimand Definition

To assess the primary objective, the treatment policy estimand is defined by the following key attributes:

- Population: Subjects in the randomized population
- Assessment: Worst pain and average pain within the last 12 hours as assessed by the spontaneous NRS score
- Variables (Endpoints): Described in table below
- Population-level summary (estimate of the treatment effect): Described in table below

Variables (Endpoints)	Population-level summary (estimate of the treatment effect)
Time to onset i.e. time to decrease from baseline of two points in the spontaneous NRS score. *Derivation:* First scheduled time point for which the change from baseline is ≤ - 2 points.	The number (%) of subjects who reach the time to onset in each treatment group. The mean time to onset in each treatment group
Peak effect i.e. maximal decrease from baseline in the spontaneous NRS score. *Derivation:* Minimum change from baseline amongst the scheduled timepoints	The mean peak in each treatment group
Time to peak-effect i.e. time to reach the peak-effect *Derivation:* First timepoint for which the peak effect is reached	The mean time to reach the peak-effect in each treatment group
Duration of effect (in days) i.e. duration between time to onset and last timepoint with decrease from baseline in the spontaneous NRS score is ≥ two points *Derivation:* Duration is calculated as: last timepoints for which change from baseline ≤ -2 – time to onset (in days)	The mean duration of effect in each treatment group (for the subjects who reach the time to onset)

Each endpoint will be evaluated using the worst pain within the last 12 hours and using the averaged pain within the last 12 hours.

5.7.3.2 Primary Analysis

For each estimate, analysis will be based on the treatment policy estimand: No adjustment will be made in case of intake of rescue medication. No handling of missing data will be performed in the primary analysis.

Listings will be provided including all subjects with missing values for the 4 primary endpoints based on the NRS score. For subjects with missing values, the listings will provide all observed data related to the primary endpoints i.e. all measurements recorded prior to the missing value, any measurements recorded after the missing value, important baseline characteristics, the reason for study discontinuation and the timing of study discontinuation.

Summary table for time to onset, peak-effect, time to peak effect and duration of effect will be computed for each assessment, by treatment group and Placebo versus all Dysport groups.

The number and percentage of subjects who reach the time to onset will be presented for each assessment, by treatment group.

For each assessment, scatter plots and box whisker plots will be generated for the comparison of the peak effects between the treatment groups and all Dysport groups.

5.7.3.3 Sensitivity Analysis

The same analyses as described in section 5.7.3.2 will be performed on the PP population using the uncorrected parameters if important differences, i.e. at least 2 patients in the same treatment group, between the randomised population and the PP population are observed: the need for this analysis will be discussed during the blind data review meeting.

5.7.3.4 Supplementary Analysis

Not applicable.

5.7.3.5 Subgroup Analysis

No subgroup analyses will be performed.

5.7.4 Randomised double-blind period: Analysis of Key Secondary Efficacy Endpoints

5.7.4.1 Endpoint, Treatment Effect and Estimand Definition

To assess the secondary objectives, the treatment policy estimand is defined by the following key attributes:

- Population: Subjects in the randomised population
- Assessments: Described in table below
- Variables (Endpoints): Described in table below

- Population-level summary (estimate of the treatment effect): Described in table below

Assessment	Variables (Endpoints)
Spontaneous pain as assessed by the spontaneous NRS score	Change from baseline in the spontaneous NRS score to each schedule timepoint
Stimulus evoked pain as assessed by the NRS score during QST	Change from baseline in the stimulus evoked NRS score to each scheduled timepoint

Spontaneous NRS Score

For each visit, spontaneous NRS (average and worst pain) score is assessed twice per day. The 2 assessments will be described separately as well as the daily average (mean of the NRS score assessed in the morning and in the evening) for the average NRS and the daily worst value for the worst NRS scores (worst NRS score assessed by day).

Baseline will be derived as defined in section 5.1.3.

To support the analyses of NRS score, the following endpoints will be considered:

- Time weighted Sum Pain Intensity Differences (SPID) from time 0 to each visit:

  $SPID_{0\text{-}Wx} = \sum_{i=0}^{i=n} CHG_i\,(t_{i+1} - t_i)$ where t_0 is the baseline time, t_i is the scheduled assessment time and CHG_i is the change from baseline in pain intensity at each post-dose scheduled timepoint.
- Sum Pain Intensity Differences Area Calculation (Area Under the Effect (AUE)):

  $AUE_{0\text{-}Wx} = \sum_{i=0}^{i=n(}(CHG_i + CHG_{i+1})/2) * (t_{i+1} - t_i)$ where t_0 is the baseline, t_i is the scheduled assessment time and CHG_i is the change from baseline in pain intensity at each post-dose scheduled timepoint.

SPID and AUE will be evaluated at each visit (Week 6, Week 12 and end of study) using the worst pain within the last 12 hours and using the average pain within the last 12 hours, based on the spontaneous NRS score.

Painful Area Mapping

Painful area mapping includes longitudinal axis (cm) and total painful area (cm^2). It is assessed at screening, injection test 1 and 2, baseline, day 1 pre-dose, week 6, week 12 and end of study. Change from baseline will be derived for each parameter.

QST

The stimulus evoked NRS score is assessed during QST at baseline (day -7 day -1), week 6 and week 12, and include the following parameters:

- **Baseline assessment** on contralateral/non-painful area on painful area: NRS assessment is performed on each area (baseline assessments).

  Change from baseline will also be derived at each timepoint for baseline assessment, for the painful area only.

- **Temporal summation** on painful area only: NRS score is recorded pre-stimulus and 10 attempts are performed after stimulus.
  Change from baseline will also be derived at each time point as follows: NRS score from the last set of attempts – NRS pre-stimulation.

- **Tactile detection thresholds** on contralateral/non-painful area and on painful area: results (in g) will be assessed to determine sensory and pain perception threshold on each area.
  Thresholds are assessed on a logarithmic scale. It will be converted to a linear scale for the analysis (see section 7).
  Change from baseline will also be derived at each time point, for the painful area only.

- **Mechanical pain sensitivity and dynamic mechanical allodynia** on contralateral/non-painful area and on painful area: on each area, NRS-score will be assessed during static mechanical allodynia and dynamic mechanical allodynia.
  Change from baseline will be derived at each time point, for the painful area only.

- **Pressure pain thresholds (PPT) (in kg/cm²)** on contralateral/non-painful area and on painful site: 3 readings of PPT, as well as their average, will be assessed in 4 positions, on each area. The global average of all the PPT values from all the positions will be derived for the painful and non-painful area.
  Change from baseline on the global average PPT will also be derived for the painful area only.

- **Conditioned pain modulation** (CPM) on painful area will be performed and the following parameters will be determined:
  a. 2 NRS scores: baseline and resulting NRS (cuff in situ).
  b. Duration of cuff occlusion (in min:sec)
  c. Clenching (Yes/No)
  d. Pressure applied (in mmHg)
  e. 3 PPT readings (in kg/cm²) and their average.

  CPM is assessed at the point on the painful area with the lowest PPT value from the previous test. A flag should be added if CPM is not evaluated at the lowest PPT position. Change from baseline on the average PPT for the painful area will also be derived.

- **Thermal detection and pain thresholds** on contralateral/non-painful area and on painful area including cold sensation (in °C; 4 replicates and the average), warm sensation (in °C; 4 replicates and the average), cold pain (in °C; 3 replicates and the average) and heat pain (in °C; 3 replicates and the average).
  For each subject, the number of incorrect perception of temperature by test will be derived for the painful and non-painful area.

Temperatures below or equal to 0°C and temperatures above or equal to 50°C are not reliable for the analyses and therefore will be excluded from the statistical analyses.

5.7.4.2 Main Secondary Analysis

For each estimate, analysis will be based on the treatment policy estimand: No adjustment will be made in case of intake of rescue medication.

Painful Area Mapping

Summary table for raw data and changes from baseline of the longitudinal axis and the total painful area will be provided by treatment group and measurement time and Placebo versus all Dysport groups by measurement time.

Spontaneous NRS scores

Each analysis on the spontaneous NRS score will be produced separately for the Average Numeric Pain Rating and the Worst Numeric Pain Rating.

Summary table for raw data and changes from baseline in the spontaneous NRS score will be produced by treatment group, and measurement times, only for the daily average for the average NRS scores and for the daily worst for the worst NRS scores).

The graph of arithmetic mean ± SD over time will be provided for the change from baseline in the spontaneous NRS score (daily average for the average NRS and the daily worst for the worst NRS) with all treatment groups on the same graph. Size groups at each time point will also be presented on the graph.

The graph of arithmetic mean ± SD over time will be provided for the change from baseline for the morning score and evening score on the same graph, separately for each treatment group.

Individual raw data and change from baseline spontaneous NRS score versus time profiles will be presented graphically for each subject with the worst numeric pain rating within the last 12 hours and the average numeric pain rating within the last 12 hours on the same graph.

Listings of individual data of the spontaneous NRS scores will be provided including all subjects with missing data. Values measured on a day where a rescue medication was taken will be flagged.

Summary table for SPID and AUE parameters will be computed for each assessment, by treatment group and visit.
For each assessment, scatter plots and box whisker plots will be generated for the comparison of SPID and AUE between the treatment groups.

Listing of individuals values of SPID and AUE will be provided.

OST analyses

Baseline assessments

Summary tables for raw data and changes from baseline in the NRS score will be produced by treatment group and measurement times.

Scatter plots of individual values at each time point will be presented with the arithmetic means by time point, linked by treatment group. All treatment groups will be presented on the same graph.
Individual values-time profiles (spaghetti plots) will also be presented for each treatment group on linear scale.
For the baseline assessments, individual histograms of the raw values of the NRS score will be provided to compare non-painful area with the painful area, for each measurement times. Values at painful and non-painful areas will be presented on the same graph.

Tactile detection thresholds

For each test (sensory threshold and pain perception threshold), summary tables for raw data and changes from baseline will be produced by treatment group and measurement times.
For the painful area, scatter plots of Von Frey sensory threshold and pain perception threshold will be provided with arithmetic means linked between the visits for each group. All treatment groups will be presented on the same graph.

Individual values-time profiles (spaghetti plots) for each test will also be presented for each treatment group on linear scale.

For each test, individual histogram will be provided: for each subject, the Von Frey reference will be represented at each time point for the painful area and the non-painful area on the same graph. For each value, the associated force value will be presented on the graph.

Mechanical pain sensitivity and dynamic mechanical allodynia

For each test (static mechanical allodynia and dynamic mechanical allodynia), summary tables for raw data and changes from baseline in the stimulus-evoked NRS scores will be produced by treatment group and measurement times.

For each test, for the painful area, scatter plots of stimulus-evoked NRS scores will be provided with arithmetic means linked between the visits for each group. All treatment groups will be presented on the same graph.

Individual NRS score-time profiles (spaghetti plots) for each test will also be presented for each treatment group on linear scale.

For each test (static mechanical allodynia and dynamic mechanical allodynia), individual histogram will be provided: for each subject, the raw NRS data will be

represented at each time point for the painful area and the non-painful area on the same graph.

Temporal summation at painful area

Summary tables for the pre-stimulus NRS score and the 10 attempts post-stimulation will be provided for raw data by treatment group and measurement times. Summary tables will also be provided for change from baseline by treatment group and measurements.
The number of repetitions will also be described by treatment group and measurement times.

The graph of arithmetic means according to the stimulation set numbers will also be provided for each treatment group with all visits on the same graph. Treatment groups will be presented on separated graph.

Individual graphs of the NRS-score profile (pre-stimulus and post-stimulus) will also be provided, with all visits on the same graph: raw NRS score will be displayed (y-axis) according to the stimulation set number (x-axis). The Von Frey filaments used (von Frey Reference) will be indicated on each individual graph.

Pressure pain thresholds (PPT)

Summary tables of raw data and changes from baseline (only for the painful area) for the global average PPT will be produced by treatment group and measurement times.
For the painful area, scatter plots of the global average PPT will be provided with arithmetic means linked between the visits for each group. All treatment groups will be presented on the same graph.

Individual values-time profiles (spaghetti plots) for the global average PPT will also be presented for each treatment group on linear scale.

Individual histogram of the average pressure at each timepoint will be provided. Values for painful and non-painful area will be represented on the same graph.

Conditioned pain modulation

Average raw data and change from baseline will be described by treatment group and measurement times. Average PPT measured during previous test, at the same position as the CPM will also be described in this table.

Box-whisker plots will be generated for the comparison of CPM and PPT between treatment groups.

Individual histogram of the average PPT measured during CPM on the painful area and the average PPT measured during the previous test, at the same position on the painful area at each timepoint will be provided. Footnote will be added if CPM is

not evaluated at the lowest PPT position. Position chosen will be reported for each time point.

Thermal detection and pain thresholds

For each test (cold sensation, warm sensation, cold pain and warm pain), average raw data will be described by treatment group and measurement times.
For each test, summary tables of the correctness of the answers will also be provided by treatment group and measurement times.
For each test, for the painful area, scatter plots of the average sensation temperature will be provided with arithmetic means linked between the visits for each group. All treatment groups will be presented on the same graph.

Summary table with the number of subjects with not done assessments will be provided with the reason for not done, by treatment group and measurement times. Subjects with excluded values (values ≤0 and values ≥50) will be included in this table with the reason 'Values excluded from analyses as threshold exceeded'.

Individual average sensation temperature-time profiles (spaghetti plots) for each test will also be presented for each treatment group on linear scale.

For each test, individual histogram of the average temperature for the change sensation will be provided at each time point. Values at painful and non-painful area will be presented on the same graph.

A listing of the number of incorrect perception of temperature will be provided.

All categories for QST

Listings of individual assessments performed during QST will be provided by category of QST.

5.7.4.3 Sensitivity Analysis

No sensitivity analysis will be performed.

5.7.4.4 Subgroup Analysis

No subgroup analyses will be performed.

5.7.5 Randomised double-blind period: Analysis of Other Secondary Efficacy Endpoints

5.7.5.1 Endpoint, Treatment Effect and Estimand Definition

To assess the exploratory objectives, the treatment policy estimand is defined by the following key attributes:

- Population: Subjects in the randomized population
- Assessments: Described in table below
- Variables (Endpoints): Described in table below

- Intercurrent event: None
- Population-level summary (estimate of the treatment effect): Described in table below

Assessment	Variables (Endpoints)	Population-level summary (estimate of the treatment effect)
QoL assessed by the SF-36 questionnaire	Change from baseline in SF-36 scores at each scheduled timepoint	Difference between each Dysport doses and the placebo group in the SF-36 scores at each scheduled timepoint
Use of rescue medication during the study	Amount of rescue medication taken during the study	Difference between each Dysport doses and the placebo group, in amount of rescue medication intake during Part B
Use of rescue medication during the study	Time to first intake of rescue medication in days *Derivation:* Difference in days between date of the first intake of rescue medication and date of IMP administration.	Difference between each Dysport doses and the placebo group, in the time to first intake of rescue medication during Part B

Quality of life

QoL is assessed at day -1, week 6 and week 12 by the SF-36 questionnaire. The SF-36 consists of 36 questions divided in 9 scaled scores: General health, Reported health transition, Physical functioning, Role physical, Role emotional, Social functioning, Bodily pain, Vitality, Mental health. For more details about the derivation of the scores, see section 7. Two versions of the questionnaire were used in the study, mapping was performed to homogenize the answers, see section 7 for details about mapping rules.

In addition, a global score per patient will be derived as the sum of the individual scores at each question. It will range from 0 to 3600.

Rescue Medication

Rescue medications will be coded using the latest version of WHO-DD in effect within IPSEN at the time of database lock.

The total amount of rescue medication will be derived.

5.7.5.2 Analysis

Quality of Life

A listing of individual responses to the SF-36 questionnaire will be prepared.

For each question of the SF-36 questionnaire, a summary table presenting the raw scores and change from baseline will be generated by dimension, treatment group and measurement time.

Arithmetic means of the global scores will be presented on a histogram by treatment group, with all visits and dimensions on the same graph. Arithmetic means of the

global scores will also be presented on a histogram by dimension, with all visits and treatment group on the same graph.
Individual histograms presenting mean scores by dimension and visit will be produced, with all dimensions on the same graph.

Rescue Medications
A listing of rescue medications will be provided, including the total amount of rescue medication and the time from D1 to first intake of rescue medication.

Summary of count and percentages of subjects having at least one rescue medication will be provided by ATC class and preferred Name, by treatment group.
Summaries of the total amount of rescue medication by preferred Name and the time to first intake (in days) will be provided by treatment group and Placebo group versus all Dysport groups. The number of subjects using a rescue medication and the number of rescue medication taken will also be described by treatment group.

5.8 Safety

5.8.1 General Consideration

All safety summaries and analyses will be based upon the Safety population. All safety data will be included in subject data listings (see listing detail conventions in Appendix A5). There will be no statistical comparison between the treatment groups for safety data.
If conversion factors are used, they should be presented either in the relevant section or a link to section 7 should be added.

5.8.2 Extent of exposure

In Part B, duration of exposure will be defined in weeks as:
([date of last visit attended – first IMP injection date] +1)/7.

The total dose received will be derived as followed:
- Total Dose (in U) = Number of injection site*Number of units of Dysport received,
- Total dose (in U/cm²) = Total dose / (Total painful area at day 1 pre-dose).

The following extent of exposure summaries will be presented for Part B, by treatment group and all Dysport:
- Summary of the number of injections sites,
- Summary of the volume injected (total and per site),
- Summary of the total dose received by treatment group,
- Summary of the total dose in U/cm² received by treatment group.

The following extent of exposure listings will be presented for Part A and Part B:
- Listing of exposure data (Part B only),
- Listing of subjects receiving test drugs from different batches.

5.8.3 Adverse Events

All adverse events (AEs) recorded in the eCRF will be coded using the latest version of MedDRA dictionary in effect within IPSEN at the time of the database lock. AEs will be classified as treatment-emergent AEs (TEAEs) according to the rules below:

- Events with start date and time on or after the date and time of IMP administration in Part B and up to End of Study (EoS) visit or Early Discontinuation (ED).
- Events whose severity worsens on or after the date and time of IMP administration in Part B and up to EoS visit or ED visit,
- Refer to appendix A3 for handling of partial date. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

The following summary will be provided by total dose and treatment group (i.e. by injection site dose) and all Dysport for Part B:

- An overview table summarizing the number and percentage of subjects with at least one of the following AEs: any AE; any TEAE; any severe TEAE; treatment-related TEAE; TEAE leading to discontinuation from the study, Serious TEAE, treatment-related Serious TEAE, Serious TEAE leading to death, treatment-related Serious TEAE leading to death, Serious TEAE leading to discontinuation from the study, any Adverse Events of Special Interest (AESI). The ranges to use for the dose will be precisely defined during the data review meeting.

The following summaries will be provided for Part B by treatment group and all Dysport groups:

- A summary of the number and percentage of subjects reporting a TEAE by treatment group, SOC and PT,
- A summary of the number and percentage of subjects reporting a TEAE by treatment group and PT,
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, causality, SOC and PT,
- A summary of non-serious TEAE by treatment group, SOC and PT.

AEs summaries will be ordered in term of decreasing frequency for SOC and PT within SOC in the treatment group (Part B) and then similarly by decreasing frequency in the treatment group, and then alphabetically for SOC and PT within SOC.

AEs will be counted as follows:

- Subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE coding to a particular PT are counted only once for that PT;
- Subjects reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case severity will be used in the corresponding severity summaries;

- Subjects reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case relationship to study medication will be used in the corresponding relationship summaries;
- If the severity is missing for a TEAE, it will be considered as missing in the summary tables;
- If the causality is missing for a TEAE, it will be considered missing in the summary tables;
- The non-serious TEAEs table should include a specific row "any non-serious TEAE above x%".

In addition, for each part, a listing with all AEs data will be listed by treatment group including non-TEAEs, Treatment-emergence status will be flagged in the listing, and AESI will also be flagged.

Deaths, Serious Adverse Events, and Other Significant Adverse Events

Adverse events of special interest (AESIs) for IMP Dysport are TEAEs that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity like reactions. TEAEs due to possible remote spread of the effects of IMP Dysport will be identified using the list of MedDRA PTs compatible with the mechanism of action of BTX-A and based on the recommendations from the Committee for Medicinal Products for Human Use (CHMP) and the Food and Drug Administration (FDA). TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions. A list of MedDRA preferred terms, used to identify any potential AESI, is provided in a separate document AESIs MedDRA version 21.1.xlsx dated 02 April 2019.
All TEAEs identified using the search strategy described above will be medically evaluated during the study, before the database lock and unblinding, by the sponsor to identify events which could possibly represent 'remote spread of effect of toxin', or which are suggestive of 'hypersensitivity reactions' due to study treatment administration. Cases will be excluded if they are confounded by presence of alternative clinical etiologies (medical history, concomitant medication or diagnosis which could account for the symptoms); if they are considered to be local effects instead of distant spread as judged by the site of injection; the time period between the last study treatment administration and event onset is not in accordance with the expected mechanism of action; or due to insufficient information/evidence to make an assessment.
In the summaries, only the final list of AESIs confirmed by the sponsor as "a possible remote spread event" or "hypersensitivity reactions" will be taken into account.
The following table will be presented:
- AESIs with the number and percentage of subjects and the number of occurrences presented by primary SOC and PT, presented by type of AESI.

The following listings will be provided:
- A listing of all deaths that occurred during the study,
- A listing of all serious adverse events,
- A listing of all adverse events leading to discontinuation of study,

- A listing of subjects having AESIs.

5.8.4 Laboratory Data

All laboratory data will be presented in the units of International System of Units (SI).

The following laboratory parameters will be taken at screening:

- **Chemistry:** Albumin, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Bicarbonate, Direct Bilirubin, Bilirubin, Calcium, Cholesterol, Creatine Kinase, Chloride, Creatinine, C Reactive Protein, Gamma Glutamyl Transferase (GGT), Glucose, Potassium, Phosphate, Protein, Sodium, Triglycerides, Urea
- **Haematology:** Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Monocytes, Neutrophils, Platelets, Erythrocytes, Leukocytes
- **Urinalysis (Qualitative):** Bilirubin, Glucose, Ketones, Nitrite, Occult Blood, pH, Protein, Urobilinogen

In addition, the following listings are to be provided for Part A and Part B:

- Listings of all laboratory data (haematology, clinical chemistry and urinalysis). Out-of-reference-range values will be flagged as high (H) or low (L), or clinically significant (CS). Any unscheduled laboratory assessments will be flagged [U] in the listings.
- Laboratory reference ranges (by gender and age where relevant).

5.8.5 Vital Signs

The following Vital signs parameters will be taken in supine position at screening, injection test 1 and 2, baseline, day 1 pre-dose, day 1 post-dose, week 6 and end of study and in standing position at screening only:

- Systolic blood pressure (mmHg),
- Diastolic blood pressure (mmHg),
- Heart rate (beats/min).

The following summaries are to be provided for Part B:

- A summary of the actual and change from baseline (only for supine position) in each vital sign parameter (systolic blood pressure, diastolic blood pressure and heart rate) by treatment group and timepoint,

The following listings are to be provided (Part A and Part B):

- A listing of vital signs data by treatment group, with PCSA values highlighted. PCSA criteria are defined in appendix A2. Any unscheduled vital signs will be flagged [U] in the listing.

5.8.6 Electrocardiogram (ECG)

Results from the local ECG, assessed at screening, will be used.

An overall Investigator assessment of ECG will be provided as "normal", "abnormal, not clinically significant" and "abnormal, clinically significant". Only investigator assessment and findings (if any) will be recorded in the database.

A summary of the investigator's interpretation will be provided for Part B.
For Part A and Part B, the investigator's interpretation will be listed with abnormal findings, if any.

5.8.7 Physical Examination

Physical examinations include a general inspection, assessed at screening, baseline, day 1 pre-dose, week 6 and end of study and a scar physical examination, assessed at week 6.

Scar physical examination will be coded using the latest version of MedDRA in effect within IPSEN at the time of database lock

The following listings will be provided on Part B:
- A listing of physical examination data,
- A listing of scar physical examination data,
- A listing presenting subjects with at least one physical examination abnormality.

5.8.8 Pregnancy tests

Urine pregnancy tests will be performed at screening, at day 1 pre-dose and at end-of-study visit.

A listing with the date of examination, the status of the examination (performed/not performed) and the result (positive/negative) will be provided by treatment group, subject and examination date.

5.9 Pharmacokinetics (if applicable)

Not applicable.

5.10 Anti-drug Antibodies (if applicable)

Not applicable.

6 DATA HANDLING

6.1 Visit window

Visits can occur +/- three days around the scheduled date.

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine abnormal laboratory, vital signs values or ECG.
If a value requires a retest (for laboratory values, vital signs and ECG) the closest non-missing reliable value to the scheduled visit will be used in the summary tables.
An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of likely values.
Subjects who have withdrawn early from the study have their last assessment entered as visit 90 in the eCRF. By convention, for these subjects, the visit number will be reassigned to the next empty visit number (i.e. if a subject has Visit 1, 2, 3 and 90 entered in the database, the visit number 90 will be reassigned to visit number 4).

7 DERIVED DATA

QST data – Tactile detection thresholds

During the tactile detection test, the force (in g) recorded is in a logarithmic scale. To analyse the data, the values will be converted on a linear scale following the table below.

Filament	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
Force (g)	0.008	0.02	0.04	0.07	0.16	0.4	0.6	1	1.4	2	4	6	8	10	15	26	60	100	180	300
Conversion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

SF-36 Questionnaire – Score derivation

The SF-36 consists of 36 questions divided in 8 dimensions: General health, Physical functioning, Role physical, Role emotional, Social functioning, Bodily pain, Vitality, Mental health and one additional question on Reported health transition.

In each dimension, each question will be coded from 0 to 100, using the table below.

Question number	Original response	Analysis Value
1, 2, 6, 8, 11b, 11d	First modality: Excellent / Much better now than one year ago / Not at All / Definitely true	100
	Second modality: Very good / Somewhat better now than one year ago / Slightly / A little bit / Mostly true	75
	Third modality: Good / About the same / Moderately / Don't know	50
	Fourth modality: Fair / Somewhat worse than one year ago / Quite a bit / Mostly false	25
	Fifth modality: Poor / Much worse now than one year ago / Extremely / Definitely false	0
3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	First modality: Yes, Limited a Lot	0
	Second Modality: Yes, Limited a little	50
	Third modality: No, Not Limited at All	100
4a, 4b, 4c, 4d, 5a, 5b, 5c	First modality: Yes	0
	Second modality: No	100
7, 9a, 9d, 9e, 9h	First modality: None / All of the time	100
	Second modality: Very mild / Most of the time	80
	Third modality: Mild / A good bit of the time	60
	Fourth modality: Moderate / Some of the time	40
	Fifth modality: Severe / A little of the time	20
	Sixth modality: Very severe / None of the time	0
9b, 9c, 9f, 9g, 9i	First modality: All of the time	0
	Second modality: Most of the time	20
	Third modality: A good bit of the time	40
	Fourth modality: Some of the time	60
	Fifth modality: A little of the time	80
	Sixth modality: None of the time	100
10, 11a, 11c	First modality: All of the time / Definitely true	0
	Second modality: Most of the time / Mostly true	25
	Third modality: Some of the time / Don't know	50
	Fourth modality: A little of the time / Mostly false	75
	Fifth modality: None of the time / Definitely false	100

Within each dimension, scores will be derived as the mean of the responses, thus scores will range from 0 to 100, with higher score defining a more favourable health. Missing data will not be taken into account and will not be replaced. Table below presents the number of questions by dimension.

Area	Dimension	Numbers of questions
Functional status	Physical functioning	10
	Social functioning	2
	Role physical	4
	Role Emotional	3
Wellbeing	Mental health	5
	Vitality	4
	Bodily pain	2
Overall evaluation of health	General Health	5
	Reported health transition	1
TOTAL		*36*

SF-36 Questionnaire – Mapping rules between Version 2.0 and 1.0

Question	Version 2	Version 1	Mapping rules
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	Modalities used are the following: - All of the time - Most of the time - Some of the time - A little of the time - None of the time	Modalities used are the following: - Yes - No	Modalities from version 1 will be mapped as follow: - All of the time => Yes - Most of the time => Yes - Some of the time => Yes - A little of the time => Yes - None of the time => No
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	Modalities used are the following: - All of the time - Most of the time - Some of the time - A little of the time - None of the time	Modalities used are the following: - Yes - No	Modalities from version 1 will be mapped as follow: - All of the time => Yes - Most of the time => Yes - Some of the time => Yes - A little of the time => Yes - None of the time => No
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.	Modalities used are the following: - All of the time - Most of the time - Some of the time - A little of the time - None of the time	Modalities used are the following: - All of the time - Most of the time - A good bit of the time - Some of the time - A little of the time - None of the Time	No change will be done

8 REFERENCES

Reference to ICH regulatory guidelines:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E6: Good Clinical Practice
- ICH E9: Statistical Principles for Clinical Trials
- ICH E9 (R1) Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Reference to European Medicines Agency (EMA) or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials
- Choice of a non-inferiority margin
- Clinical trials in small populations
- Data monitoring committees
- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials
- Application with Meta Analyses, One pivotal study
- Multiplicity issues in clinical trials
- Switching between superiority and non-inferiority
- Guideline on the clinical development of medicinal products intended for the treatment of pain

Reference to FDA guidelines:

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Standard SDTM+ user guide

References for guidance on analysing pain response:

- Standard Methods for Analysis and Reporting of VAS or NRS Derived Pain Relief Response Scores

9 APPENDICES

A1. SAS code

Not applicable

A2. Normal ranges

Normal ranges for Vital Signs parameters (Males/Females from 18 to 65 years old):

Parameter	Normal ranges
Systolic Blood Pressure	≤ 95 mmHg ≥ 150 mmHg
Diastolic Blood Pressure	≤ 60 mmHg ≥ 90
Heart Rate	≤ 51 ≥ 100
Body Temperature	≤ 35.5 ≥ 37.5

Normal ranges refer to ranges agreed with the clinical site.

A3.Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / partial, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the first IMP administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

Algorithm for Prior/ Concomitant

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only.
In case of partial start and/or stop medication/ non-drug therapies/surgical procedures dates, imputation will be done to determine the classification:

- If a partial start date, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, will be classified as concomitant.

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done (for AE start date only assuming no AE end date are missing). The date imputation algorithm for incomplete adverse event start dates is described in Table 1. Classification of adverse event according to its treatment-emergent status is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose First IMP administration = 2002-08-11 and several AEs have incomplete start dates.

Table 1 Data imputation algorithm for AE start date (AESTDT)

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

In the pre-randomisation run-in period, the same algorithm as above will be followed using the first IMP administration of each period as reference date for the imputation.

If AE end date is partial, imputation could be done assuming the latest possible date (i.e. last day of month if day unknown, or 31st of December if day and month are unknown).

A4. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5 …) must be decimal justified.

The mean, median, lower quartile, upper quartile, SD and standard errors of the mean (SE), 95% confidence interval values will be reported to one decimal place greater than the raw data recorded in the database.
The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database.
In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator will be specified in a footnote for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but in the CSR only frequencies should be described.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. For each safety parameter for which it is possible to have values below or above Limit Of Quantification (LOQ), the rule to be used in the statistical tables is to replace values below or above a limit of quantification by LOQ.

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

A5. Listings conventions

Any listings will contain at least the following data: subject identifier, age and gender. When dates are presented, the associated study days should be included. They should be sorted by treatment group then subject identifier. For multicentre studies, listings should be broken down by centre and treatment group.

A6. EudraCT categories for age

For EudraCT results summaries, in addition to quantitative descriptive statistics of age, demographic tables should include presentation of age using the following EudraCT categories (as applicable):

In utero
Preterm newborn - gestational age < 37 weeks
Newborns (0-27 days)
Infants and toddlers (28 days-23 months)
Children (2-11 years)
Adolescents (12-17 years)
Adults (18-64 years)
From 65 to 84 years
85 years and over