Title: An Observational, Single-Arm Study to Describe Pain Intensity, Pain Relief and Safety of Neosaldina® in the Treatment of Tension-Type Headaches in Healthy Subjects

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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Statistical Analysis Plan

AN OBSERVATIONAL, SINGLE-ARM STUDY TO DESCRIBE PAIN INTENSITY, PAIN RELIEF AND SAFETY OF NEOSALDINA® IN THE TREATMENT OF TENSION-TYPE HEADACHES IN HEALTHY SUBJECTS

Prepared for:

Sponsor Name: Takeda Distribuidora Ltda

Study number: Neosaldina-5001 MyHead

Document developed based on Protocol version: 1.0 of protocol: 27-july-2018

Case Report Form version used:

Date Statistical Analysis Plan approved:

	Name	Responsibility	Signature	Date
Preparation by	PPD	Epidemiologist	PPD	10/04/2019

	Name	Responsibility	Signature	Date
Approval	PPD	Engagement Manager	PPD	10/4/19

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Events
DSM–5	Statistical Manual of Mental Disorders
EC	European Commission
eCRF	Electronic Case Report Form
GPP	Good Pharmacovigilance Practice
PGA	Patient global assessments
PID	Pain Intensity Difference
PR	Pain Relief
SPID	Sum of Pain Intensity Difference
SSR	Special Situation Report
TTH	Tension-Type Headaches

1. STUDY OBJECTIVES

1.1 Primary Objectives

- To describe pain relief in tension-type headaches (TTH) with Neosaldina® treatment.

1.2 Secondary Objectives

- To determine the safety of Neosaldina® in TTH.
- To assess treatment satisfaction of Neosaldina® in TTH.

1.3 Exploratory Objectives

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2. STUDY DESIGN

2.1 Study Type

This study is a 'non-interventional study' as defined in Directive 2001/20/EC and will follow the guidelines for GPP.

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.

- Neosaldina® is prescribed in accordance with the terms of the marketing authorization(s).
- The prescription of Neosaldina® is clearly separated from the decision to include the subject in the study.

The principal investigator and sub-investigator will observe and assess each participant from the time of informed consent through the completion of observation according to the procedures depicted in section 6.6 of the protocol.

2.2 Study scope and information sources

The study is planned to be conducted in five sites in Brazil. As TTH is not usually the reason for seeking a doctor, the study will be conducted in clinics with specialists who usually treat the general population with non-serious conditions (general practitioner, and gynecologists, for instance). The Sponsor will keep a record of the individuals responsible for each participating Study Site, the Site Responsible.

The study variables will be recorded in a specially designed electronic case report form (eCRF). Data will be compiled from patient medical records and patient visits by the investigators and will be transferred to the eCRFs.

2.3 Sample Selection

A total of 317 patients will be recruited. The sample size rationale was based on the primary endpoint. Thus, the calculation was performed in order to estimate a mean in a finite population. Using an expected standard deviation of 3,00, an error of ± 0.5 a drop-out rate of 45% and a screen failure rate of 20%, 317 patients would be necessary to achieve a

robust estimation of the population mean (95% Confidence Interval, level of significance 0.05).

The patients should satisfy all the inclusion criteria and none of the exclusion criteria. All patients participating in the study should sign the informed consent at the baseline visit and prior to inclusion.

Inclusion criteria/evaluable cases

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Confirmed diagnosis of episodic TTH, as determined by the International Classification of Headache Disorders
4. Healthy subjects who were prescribed 2 tablets of Neosaldina® for episodic TTH.
5. The subject is at least 18 years old.
6. Patients receive treatment according to the Summary of Product Characteristics for Neosaldina®.
7. Patients able to swallow capsules or tolerate oral medications.
8. Patients with access to a mobile phone with the ability to download the app with the study questionnaire.
9. Patients who have at least one episode of TTH per month.

Exclusion criteria/non-evaluable cases

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Currently participates or plans to participate in an interventional clinical trial.
2. Patients who have hypersensitivity or intolerance to dypirone (or pyrazolonic derivatives) or other components of the product formula.
3. Patients with a history of migraine, cluster headaches, chronic TTH or any other type of primary headache other than episodic TTH.
4. Patients with suspected secondary headache.
5. Patient with serious comorbidities (hypertension, blood dyscrasias, malignant neoplasms, any type of hepatitis or kidney disease, disorders of the hematopoietic system, insufficient function of the bone marrow or certain metabolic diseases, such as hepatic porphyria or congenital deficiency of glucose-6-phosphate dehydrogenase) or taking any medications which might confound the pharmacological effects of the study drug (e.g. immunosuppressive drugs, and beta blockers, anticonvulsivants, antidepressants) within 30 days before the start of study.
6. Women who may be pregnant or breastfeeding during the course of the study.
7. Patients who have a history of alcohol abuse or other drugs according to Diagnostic and Statistical Manual of Mental Disorders (DSM–5).
8. Patients presenting mental incapacity, unwillingness or language barriers unable to understand the guidelines specified in this protocol.
9. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

2.4 Follow up Period

Investigators will have two follow-up phone calls to verify the patients' adherence to the protocol. These calls will be performed by site personnel in days 15 and 30. A total of 1 visit onsite and up to 2 follow-up calls will be made in the study.

After inclusion, a return visit will be schedule within 45 days from Day 1, complying with the allowed deviation (± 5 days). Patients will be instructed to insert the data in an application, downloaded onto mobile phone, whenever they had an episode of TTH and use Neosaldina® (see more information regarding data collection in the section 8.4.1). Two follow-up phone calls will be performed to verify the patients' adherence to the protocol. These calls will be performed by site personnel in days 15 and 30.

2.5 Sample Size Calculation

The sample size rationale was based on the primary endpoint. Thus, the calculation was performed in order to estimate a mean in a finite population, using the following equation:

$$mm = \frac{ZZ^{2}_{(1-\alpha\alpha)/2}{}^{2}}{dd^{2}}$$

To our best knowledge, there is no data in literature showing the results of SPID 0-2 in TTH population using Neosaldina®. However, a systematic review (19) conducted by Stephens et al (2016) reported the following mean and standard deviations for other analgesics:

Table 1 - Mean and standard deviations for other analgesics

Drugs	SPID	
	Mean	SD

Paracetamol 1000 mg	4,32	1,98
Paracetamol 1000 mg + cafeína 130 mg	4,42	1,88
Ibuprofeno 400 mg	4,56	1,73
Placebo	3,69	1,7

As these data are not related to the same studied drug, a standard deviation of 3,00 was assumed. Therefore, considering an error of ± 0.5 a dropout rate of 45% and a screen failure rate of 20%, 317 patients would be necessary to achieve a robust estimation of the population mean (95% Confidence Interval, level of significance 0.05).

2.6 Termination Criteria (if applicable)

The reasons for termination will be documented for each patient. When a patient terminates participation in the study, a final evaluation will be completed with the reasons for termination and the date.

Patients withdraw or are withdrawn from a study for any of the following reasons:

- Withdrawal of consent: subjects who for any reason withdraw the free and informed consent;
- Lost to follow-up (no return of the subject on the expected date of visit - drop-out from the protocol);
- Death;
- Study termination;
- Any situation that places the subject within one of the exclusion criteria.

2.7 Study Variables

Data will be collected from medical charts and during the routine clinical appointment. Main data collected for the study will include:

Table 2 – List of study variables

Identification variables (collected in the baseline)	Study ID Site ID Patient number Informed consent obtained date
Demographic and anthropometric variables (collected in the baseline)	Frequency of headache Medical appointment date Age Gender Ethnicity Occupation City of residence Monthly familiar income Weight Height Medical history Concomitant treatments Blood pressure
Lifestyle behaviors (collected in the baseline)	Smoking habits Alcohol consumption habits Physical activity Sleep quality and duration

	Use of bright light objects (computers, mobiles, TV, etc.) Time spent working daily Type of activities during the day in two categories: 1. Mostly seated, standing, moving 2. Making a great physical effort, using bright light objects (computers, mobiles, TV, etc.), outdoor activities, on traffic, leading with people, working in risky situations (doctors, nurses, policeman, fireman), working in noisy environments, use of ear phones and its duration.
Lifestyle behaviors (collected in every TTH episode)	Level of stress (none, moderate, high) Date of the last menstruation cycle Use of ear phones and its duration
Clinical variables (collected in every TTH episode)	Location and type of pain Time and date of onset of pain Pain intensity and characteristics
Treatment variables (collected in every TTH episode)	Intake of Neosaldina® Time of intake Number of tablets Pain intensity during 2h Time of first perceived pain relief
Treatment variables (collected in the last visit)	Treatment satisfaction according to the patient

	Treatment satisfaction according to the physician Medical history Concomitant treatments Blood pressure

3. DERIVED VARIABLES

In order to respond to the study aims, CRF variables related to some goal that can be transformed into scores or categories that are directly related with that goal should be considered.

3.1 Primary Variable

The primary endpoint will be the time-weighted sum of pain intensity difference (PID) from baseline (0 hour) to 2 hours after dosing (SPID 0-2). This outcome will be recorded at 15-minute intervals for the first 60 minutes, followed by 30 min from 1–2 hours after Neosaldina® administration and will be assessed using a 0–10 visual analogue scale (from 0 = 'no pain' to 10 = 'worst possible pain'). The relief of pain intensity will be also assessed by the pain intensity score difference [PID %] according to each time point.

3.2 Secondary Variables

- The percentage of patients who achieved a reduction of at least 1 point in intensity for each time interval

- Time to achieve 50% of pain intensity reduction
- Time to first perceptible pain relief (PR)
- Duration of pain relief (defined by the time to second intake of study medication).
- Patient global assessments (PGAs) of overall satisfaction ("very dissatisfied", "dissatisfied," "neither satisfied nor dissatisfied," "satisfied," or "very satisfied")
- Physician global assessments (PGAs) of overall satisfaction ("very dissatisfied", "dissatisfied," "neither satisfied nor dissatisfied," "satisfied," or "very satisfied").
- Incidence of adverse events after Neosaldina® administration.

3.3 Exploratory Variables

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3.4 Essential Variables

Essential variables are the variables necessary in order to be able to respond to the study objectives. For this study, the essential variable for evaluating the primary objective is

defined as Pain intensity during 2h, and the essential variables for evaluating the secondary objectives are defined as Time of first perceived pain relief. Patients for whom these variables are not available will be excluded from the study.

3.5 Demographic and Other Baseline Characteristics

The demographics, baseline characteristics and life style characteristics are: frequency of headache; medical appointment date; age; gender; ethnicity; occupation; city of residence; monthly familiar income; weight; height; medical history; concomitant treatments; blood pressure; smoking habits; alcohol consumption habits; physical activity; sleep quality and duration; use of bright light objects (computers, mobiles, TV, etc.); time spent working daily; type of activities during the day in two categories: 1.mostly seated, standing, moving 2.making a great physical effort, using bright light objects; level of stress (none, moderate, high); date of the last menstruation cycle; use of ear phones and its duration.

3.6 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical condition, including drug prescriptions and disease-specific history, any medical history relevant to the disease under study will be collected by eCRF.

3.7 Study Drug Exposure and Compliance

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol. The therapeutic approach will be performed according to regular clinical practice of the physicians.

3.8 Primary Efficacy Endpoint(s)

The primary efficacy endpoint will be the time-weighted sum of pain intensity difference (PID) from baseline (0 hour) to 2 hours after dosing (SPID 0-2). This outcome will be recorded at 15- minute intervals for the first 60 minutes, followed by 30 min from 1–2 hours after Neosaldina® administration and will be assessed using a 0–10 visual analogue scale (from 0 = 'no pain' to 10 = 'worst possible pain'). The relief of pain intensity will be also assessed by the pain intensity score difference [PID %] according to each time point.

3.9 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoint will be the time to first perceptible pain relief (PR), the duration of pain relief (defined by the time of second intake of study medication).

3.10 Adverse Events

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.
A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient

becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.

- Breastfeeding: Infant exposure from breast milk.
- Overdose: All information of any accidental or intentional overdose.
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual).
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product.
- Occupational exposure.
- Use outside the terms of the marketing authorization, also known as “off-label”.
- Use of falsified medicinal product.

A SSR should be reported even if there is no associated AE

4. STATISTICAL METHODOLOGY

4.1 Data Management

Data Management will be carried out according to a Data Management Plan, which must be written and approved before the design of the study database is finalized. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

If a subject is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the period of the first follow-up period.

The current Standard Coding Instructions for coding adverse events/reactions (MedDRA) must be followed.

The subjects will be identified in the database only by Study ID, Site ID, subject number, gender, age and ethnicity.

4.2 General Analytical Aspects

This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning, i.e. all data listed in section 2.

The results will be expressed as absolute frequencies and percentages for categorical variables, and as mean and standard deviation or medians and quartiles (25th–75th percentile) for continuous variables. The mean or median difference and 95% confidence interval (CI) will be calculated when appropriate. Normality was assessed using the Kolmogorov-Smirnov test.

Comparisons between independents means or medians will be based on the parametric test like Student's t test (or One way ANOVA: Analysis of variance) or non-parametric test like Mann-Whitney U test (Kruskal-Wallis test) for continuous variables and the chi-squared test for categorical variables or Fisher's exact test if one expected that the cell value would be less than 5 (categorical variables), depending on the number of groups that will be studied.

Comparisons between means or medians of related observations will be based on parametric test like the Student's t test (or ANOVA for repeated measures) or non-parametric

test like Wilcoxon test (Friedman's test) for continuous variables and the Mc Nemar test or Cochran Q test for categorical variables.
Binary multiple logistic regression model will be used to build a multivariate model to assess the association between the primary outcome and nominal, or ordinal, variables.
All of the variables in the univariate analysis with a p value less than 0.20 will be included as independent variables, as well as additional variables considered of clinical relevance.
All statistical tests will be two-tailed, and a p value less than 0.05 will be considered to be statistically significant. The factors most significantly associated to primary endpoint will be presented as odds ratio (OR) with 95% CI. Odds ratio is defined as the odds of an outcome will occur based on a certain exposure. The mean width of the 95% confidence interval for the analyzed proportion will be reported. All statistical analysis will be performed using R® Software. All serious AEs and/or serious issues captured in the study database and reported by the investigator to Takeda in the AER Form (according to Section 7) and all the SAEs, AEs and SSRs received directly from the patients by Takeda will be reconciled at the end of the study and will be analysed and listed/tabulated in the final report.

Collection and recording of SAEs, AEs, SSRs and PQI will commence once the study participant has provided informed consent. The investigator should notify Takeda within 1 working day of becoming aware of a SAE, or other serious events/issues that were spontaneously reported by participant. This is typically achieved by the investigator completing the adverse event report pages of an electric CRF and by submitting an AE Report Form to Takeda. Missing adverse event and concomitant medication dates are subject to recall bias, once they are patient-reported outcomes.

The Investigator may be contacted by Takeda to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested

additional information, and will notify Takeda within 1 working day of obtaining the additional information. Non-serious AEs, SSRs and PQI must be recorded in the appropriate page of the CRF.

4.2.1 Analysis Sets

Considering that this is an observational real-world study with the intention to describe the changes in the pain intensity scale, all included patients with primary endpoint data available will be included in the study analysis.

4.2.2 Primary Analysis

The primary endpoint of this study is the time-weighted sum of pain intensity difference (PID) from baseline (0 hour) to 2 hours after dosing (SPID 0-2). This outcome will be recorded at 15- minute intervals for the first 60 minutes, followed by 30 min from 1–2 hours after Neosaldina® administration and will be assessed using a 0–10 visual analogue scale (from 0 = 'no pain' to 10 = 'worst possible pain'). The relief of pain intensity will be also assessed by the pain intensity score difference [PID %] according to each time point.

As this is a descriptive study, descriptive analysis will be performed through tabulation of measures of central tendency and dispersion will be used for quantitative variables and frequency for qualitative variables.

Primary analysis population will be done using the all the complete patients included in this study.

4.2.3 Secondary and Exploratory Analyses

All the secondary endpoints will be evaluated with this is a descriptive analysis that will be performed through tabulation of measures of central tendency and dispersion will be used for quantitative variables and frequency for qualitative variables.

4.2.4 Safety Analysis

AEs will be summarized using the safety analysis set. Data will be summarized using preferred term and primary system organ class.

Summary tables for treatment-emergent AEs will include numbers and percentages of subjects experiencing AEs by system organ class and preferred term. The following summary tables will be included in the report by subject group: summary of AEs and drug-related AEs, relationship of AEs to study drug, severity of AEs and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Furthermore, safety profile will be reported by recording the frequency and severity of adverse events associated to the use of study treatments:

I. Adverse drug reactions including headache, flatulence, respiratory infection and sinusitis;
II. Adverse events with frequency >5% and 10%;
III. Serious adverse events.

No interim analysis is planned in this study.

4.2.5 Demographic and Other Baseline Characteristics

All demographic and relevant clinical characteristics variables at baseline will be described through tables with descriptive measures and appropriate graphics. Quantitative variables, such as age, will be described using measures of central tendency such as mean and median, and through measures of variability, such as standard deviation, range and interquartile difference. Qualitative variables, such as gender, will be described as absolute frequencies and percentages.

4.2.6 Medical History and Concurrent Medication

All relevant medical history and concurrent medication variables will be described through tables with descriptive measures and appropriate graphics. Quantitative variables will be described using measures of central tendency such as mean and median, and through measures of variability, such as standard deviation, range and interquartile difference. Qualitative variables will be described as absolute frequencies and percentages.

4.3 Study Population

All patients screened for the study will be grouped and presented in a final list. Patients considered not eligible for the study participation will be in the final list with the respective reason for screen failure. All patients enrolled in the study who meet the defined criteria will be included in the population analyzed in terms of the primary objective. These patients, who

will comply fully with the requirements of the protocol, will be asked to give their informed consent in writing.

4.4 Handling bias, missing values and loss of follow-up

Missing individual items within summary scales such as PROs will be handled according to the scoring directions for each scale. In the absence of scoring guidelines for missing data, the individual items will be reported as missing and the summary score itself will be considered missing. In this study, data inputting is not planned.