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

NCT Number: NCT03666858

Protocol Approve Date: 27-July-2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

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.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-Interventional Study Protocol

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

Short title: Pain intensity and Pain Relief of Neosaldina® for Tension-Type Headaches

Study ID: Neosaldina-5001

Sponsor: Takeda Distribuidora Ltda.
Rua do Estilo Barroco, 721
04709-011 - São Paulo/SP – Brazil
Phone:+ 55 11 5188 4400

Study phase: Medical Affairs, Post-Approval Company Sponsored (Observational)

Date of version 1.0 of protocol: 27-july-2018

1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	Brazil Contact
Adverse event and other PV reporting	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki (1)
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline
- Guidelines for good Pharmacoepidemiology practices (GPP) (2)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

Investigator Name

Investigator's Title

Location of Facility (City, State/Provence)

Brazil

Location of Facility (Country)

STUDY SUMMARY

Name of Sponsor(s): Takeda Distribuidora Ltda	**Compound/Product:** A dypirone (300 mg), isometheptene (30 mg) and caffeine (30 mg) product/ Neosaldina®
Title of Protocol: 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	
Study Number: Neosaldina-5001	**Phase:** 4
Study Design: National, multicenter, prospective, observational study	
Primary Objectives: To describe pain relief in tension-type headaches (TTH) with Neosaldina® treatment	
Secondary Objectives: • To determine the safety of Neosaldina® in TTH • To determine the treatment satisfaction of Neosaldina® in TTH	
Exploratory Objectives: CCI [redacted]	
Subject Population: Healthy, adults, subjects with episodic TTH	
Number of Subjects: 317 subjects	**Study Sites:** Approximately 5 sites in Brazil
Dose Level(s): Neosaldina®, a dypirone (300 mg), isometheptene (30 mg) and caffeine (30 mg) product, administered orally as 2 tablets in the beginning of the TTH episode, every 6 hours, at maximum of 8 tablets per day.	**Route of Administration:** Neosaldina® tablets by oral route
Duration of Study: Overall Study Duration: This study will have duration of around 6 months for observational phase. Enrolment period: 4 months Treatment/Follow-up: 45 days	
Criteria for Inclusion: Healthy, at least 18 years old, subjects who were prescribed 2 tablets of Neosaldina® for episodic TTH, able to swallow capsules or tolerate oral medications.	
Criteria for Exclusion: Subjects who currently participates or plans to participate in an interventional clinical trial or have hypersensitivity or intolerance to dypirone (or pyrazolonic derivatives) or other components of the product formula. History of migraines, cluster headaches, chronic TTH, any other type of primary headache other than episodic TTH or headache secondary to pathologies, 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 (e.g. immunosuppressive drugs, and beta blockers, anticonvulsivants, antidepressants) within 30 days before the start of study, which might confound the pharmacological effects of the study drug. Patients who have a history of alcohol abuse or other	

drugs. Subjects presenting mental incapacity, unwillingness or language barriers unable to understand the guidelines specified in this protocol or cooperation. Besides, women in which pregnancy or breastfeeding could not be ruled out will be excluded. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

Criteria for Evaluation and Analyses:

- The primary endpoint will be the time-weighted sum of pain intensity difference from baseline (0 hour) to 2 hours after dosing (SPID 0-2).

The secondary endpoints include:

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

CCI [redacted]

Statistical Considerations:

Descriptive analysis through tabulation of measures of central tendency and dispersion will be used for quantitative variables and frequency for qualitative variables. To compare means, the study intends to analyze the variables with normal distribution by the Student's t-test, and those with non-normal distribution by Mann-Whitney nonparametric test. The Chi-square test will be used to assess possible differences between frequencies of categorical variables. Logistic regression will be used to build a multivariate model to assess the association between the primary outcome and exposure variables.

Sample Size Justification: 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).

Table of Contents

List of Abbreviations and Definition of Terms

AE:	Adverse Event
ADR:	Adverse Drug Reaction
APP:	Application
CA:	Competent Authority
CCSI:	Core Company Safety Information
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Curriculum Vitae
DSO	Drug Safety Office
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
ICH:	International Conference on Harmonisation
ICHD:	International Classification of Headache Disorders
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
IHS:	International Headache Society
IRB:	Institutional Review Board
NSAIDs:	Nonsteroidal Anti-inflammatory Drugs
PGA:	Patient Global Assessments
PSUR:	Periodic Safety Update Report
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SPC:	Summary of Product Characteristics
SPID:	Sum of Pain Intensity Difference
TTH:	Tension-Type Headache
VAS:	Visual Analogue Scale
WHO:	World Health Organization

2 Introduction

Headache or Cephalalgia is defined as pain occurring anywhere in the region of the head or the neck representing a range of conditions (3). This group of disorders is extremely common, affecting half to three quarters of adults worldwide (4). The World Health Organization (WHO) (4) recognised it nearly 20 years ago as a global public-health priority, because it is not only painful, but also disabling (4, 5).

In Brazil it is estimated a 1-year prevalence of 70.6% for all types of headache; this figure is similar to the rates described in other countries (6). It affects people of all ages, races and socioeconomic status and is more common in women (7). The literature review performed by Queiroz et. al (2015) (6) points a 1-year prevalence of 61.6% in men and 77.8% in woman in Brazil.

Headaches are broadly divided into primary and secondary. Primary headaches refer to those without an anatomical or physiological explanation, while secondary headaches are result from underlying pathologies (5, 8). The commonly encountered primary headache disorders are migraine and tension-type headache (TTH). Migraine is usually severe, unilateral and throbbing in nature. It is often accompanied by photophobia or phonophobia, nausea and vomiting and it worsens with physical activity. TTH is characterized by bilateral location, pressing/tightening quality and of generally milder intensity compared to migraine. The accompanying symptoms of migraine (nausea, vomiting, photo- and phonophobia) are only rarely encountered in this type of headache.

The International Headache Society (IHS) had proposed clear criteria to establish subcategories among the different types of headaches. This research is focused on TTH; therefore, the International Classification of Headache Disorders (ICHD) for this type will be presented. The third edition of ICHD guideline divided TTH into episodic and chronic types. The episodic type is further divided into an infrequent and a frequent type and the main difference between them is the number of episodes; while the first occur on average <12 days/year, the latter occur ≥ 12 and <180 days/year. Episodic TTH is not associated with nausea, although the occurrence photo- or phonophobia is a possibility. Chronic TTH, on the other hand, can last hours to days, or be unremitting. Differently from episodic TTH, the chronic type may be associated with mild nausea; photo and phonophobia may also be present.

TTH is the most prevalent headache in the general population, and the second-most prevalent disorder in the world (9). It has a global lifetime prevalence of 42% in men and 49% in women. The Brazilian study performed by Queiroz and collaborators found a 1-year prevalence of 29.5% (male 28.1% and female 30.3%) (6). Although is a common condition, the precise pathogenetic mechanism of TTH is still poorly clarified (10). Evidence has grown continuously that peripheral pain mechanism plays a role in infrequent and frequent episodic types, while central pain mechanism plays a more important role in chronic type (10).

Although most of studies addressing the burden of headache focus on migraine, emerging data have been shown that the overall human cost of TTH is considerable. Song and collaborators (11) performed a study to investigate the prevalence and clinical impact of anxiety and depression among patients with TTH in the general population. As results, the authors found that these comorbidities were more prevalent in participants with TTH than in non-headache participants. In the study of Simic et al (2008) (12) patients with TTH had worse quality of life than controls.

Although simple analgesics, such as dipyrone, paracetamol (acetaminophen) or Non-steroidal anti-inflammatory drugs (NSAIDs) are often used for the treatment of TTHs and other

headaches, ergotamines, neuroleptics, opioids and combinations of analgesics are also frequently used (13). There is evidence which shows that the efficacy of simple analgesics is increased by combination with caffeine and isometheptene, which have antinociceptive activity (14).
The analgesic activity of dipyrone is undeniably proven through several clinical studies and evidence provided by the intense use in several decades. A review of its use in acute primary headaches has led to the conclusion that dipyrone is effective in the management of seizures of both tension and migraine headaches, without a significant incidence of serious adverse events or agranulocytosis (15).
The synergism of caffeine on the antinociceptive effects of dipyrone was confirmed in a study with animals (15), as well as, in humans (13) and a faster onset of action observed with the combination rather than with dipyrone alone (13).
The association of isometheptene with analgesics was considered a better alternative in the treatment of vascular headaches than ergotamine (16).
Neosaldina® acts by the action of dipyrone, isometheptene and caffeine. Dipyrone works to reduce pain sensitivity. Isometheptene acts both on the vasoconstriction of cerebral blood vessels (contributing to pain relief), as well as, on the enhancement of the analgesic and antispasmodic effect. Caffeine is a central nervous system stimulant that has a vasoconstrictor effect on cranial arteries, being useful in the treatment of headaches, especially migraines (7).

The efficacy and safety of Neosaldina® have been shown in several studies. Klapetek et al(17) performed two randomized, double-blind, trials to compare Neosadina® with the combination of ergotamine and caffeine, as well as, with placebo. Both studies showed a more consistent and constant analgesic activity with Neolsadina®. The study conducted by Forti et. al(18) showed that Neosaldina® has similar efficacy compared to combination of dihydroergotamine, caffeine, butalbital and aminophenazone.

Although the efficacy of Neosaldina® has been already demonstrated, there is still a need of evaluation related to the amplitude of pain relief derived from tension-type headaches in different ordinary lifestyle events that are commonly related to headache episodes in real world. For this reason we propose this study.

3 Study Objective(s) and Endpoint(s)

3.1 Objective(s)

3.1.1 Primary Objective

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

3.1.2 Secondary Objective(s)

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

3.1.3 Exploratory Objective(s)

CCI

[redacted]

3.2 Endpoint(s)

3.2.1 Primary Endpoint

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 assesed by the percentage pain intensity difference [PID %] in each time point.

3.2.2 Secondary Endpoints

The secondary endpoints include:

- 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 of 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.

3.2.3 Exploratory Endpoint

CCI

[redacted]

4 Study Administrative Structure

4.1 Study Sites

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 Responsibles.

4.2 Sponsor Personnel

The Sponsor will keep a record of all relevant sponsor personnel.

Name	Study Team Role
PPD	Clinical Study Manager Lead
	Clinical Research Coordinator
	Clinical Research Analyst
	Clinical Science Lead
	Clinical Science Manager
	Scientific Affairs Director - Brazil & LATAM
	Regulatory Affairs Manager
	Pharmacovigilance Manager
	Pharmacovigilance Analyst
	Pharmacovigilance Coordinator

4.3 Contract Research Organisation (CRO)

The CRO CCI will be responsible for the development of electronic tools, study implementation and monitoring, data management, data analysis and development of the final clinical study report (CSR). The CRO will keep a record of all involved CRO personnel.

5 Ethics

This study is an observational study where the existence of the study has no impact on the subject except for collection of informed consent to use of the subject's data. The study will assess patients who have already been treated with Neosaldina® and will merely observe the patient-reported outcomes. The decision to prescribe the treatment will be entirely made by the investigator.

5.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), Good Clinical

Practice (GCP), ISPE GPP guideline and any local regulations. Special attention will be paid to data protection.

The Sponsor and/or the appointed CRO will ensure that the protocol, any amendments and the Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

The sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

5.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/ IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Informed Consent Form and study questionnaire.

The appointed CRO or the Site Study Responsible will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study;
- notification of the end-of-study;
- a summary of the study results.

The Sponsor or the appointed CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

5.3 Authorities

The Sponsor or the appointed CRO will send required documents to the competent authority (CA) and/or other national or regional authorities. The Sponsor or the appointed CRO will keep an updated list of submission and approval dates and a copy of all documents submitted.

5.4 Subject Information and Written Informed Consent

The Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (and if applicable, the parent or legal guardian) can understand, and obtain the subject's (and if applicable, the

subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, parent or legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The subject must agree that sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject and parent or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.

For details, see the Informed Consent Form.

6 Study Design and Plan

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 authorisation(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.

6.1 Study Schedule

Planned Start of Study:	*Q3 2018*
Planned collection of first data point:	*Q4 2018*
Planned End of Study:	*Q1 2019*
Planned collection of the last data point:	*Q1 2019*
Planned completion of the Study Report:	*Q1 2020*

This study will have duration of around 6 months for observational phase. The Start of Study is defined as the date of first Site Initiation Visit. The recruitment period is expected to last up to 4 months. The End of study is defined as the last data point collected.
The study report should be signed within 12 months after the collection of the last data point.

The Sponsor will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB for each site, for each country and for the complete study, as locally required.

The Sponsor will ensure that results are posted on “clinicaltrials.gov” and as required by local authorities.

Based on upcoming knowledge, the Sponsor might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs and authorities will be informed promptly.

6.2 Discussion of Study Design

This is an observational, non-interventional study that aims to assess the pain intensity and pain relief of TTH after the uptake of Neosaldina®.
To avoid potential confounders, the difference between the groups, stratified by their demographic characteristics and lifestyle will also be described.

Because this is an observational study, some limitations should be minimized. To avoid selection bias, all eligible patients will be consecutively invited to the study and the enrollment period will be of 4 months.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

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 1 episode of TTH per month.

6.3.2 Exclusion Criteria

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.

6.3.3 Enrollment

Each Study Site Responsible (Investigator) should include consecutive subjects who meet eligibility criteria, from patients attending scheduled routine medical appointments.

The expected recruitment of study subjects will occur during a 4-month period. A patient tracking log form will be used by each site.

Subjects should be included in the study only once.

Data erroneously collected from subjects for which signed informed consent is not available, will not be included in or will be deleted from the database.

6.3.4 Study Discontinuation Criteria

It will be considered a premature termination the situation in which the subject discontinues the participation, i.e. they are withdrawn from the study before completing the 45 days of follow up period (± 5 days from Day 1), due to any of the reasons listed below:

1. Withdrawal of consent: subjects who for any reason withdraw the free and informed consent;
2. Lost to follow-up (no return of the subject on the expected date of visit - drop-out from the protocol);
3. Death;

4. Study termination;
5. Any situation that places the subject within one of the exclusion criteria.

6.4 Treatments

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.

6.5 Premature Termination or Suspension of Study or Investigational Site

6.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the Neosaldina® such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.6 Study Plan

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 a site personnel in days 15 and 30.

Data collection overview:

Activities	Day 1	Day 15 (+/- 3 days)	Day 30 (+/- 3 days)	Days 1-45	Day 45 (+/- 5 days)
Routine visit	X				
Informed consent	X				
Inclusion/exclusion criteria	X				
Routine physician examination, including concomitant medications and medical history	X				X
Exposure variables	X				
Follow-up 1 (phone call)		X			
Follow-up 2 (phone call)			X		
SPID[a]				X	
Pain relief[a]				X	
Duration of pain relief[a]				X	
Return visit					X
PGA overall satisfaction					X

a) For each TTH episode

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

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

Additional details about variables and types of data fields will be provided in the eCRF.

7 Safety Reporting

7.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

Adverse Drug Reactions

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.

Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Special Situation Reports

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.

Relationship of an AE to studied drug(s)

- **Related (Yes):** An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), or for which a casual relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

- **Not related (No):** An AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments. The investigator must make an assessment of causality using the above definition. Causality cannot be assumed in the absence of the investigator's assessment.:

7.2 Collection and Recording of Adverse Events, Special Situation Reports and Product Quality Issues

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.

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.

7.3 Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Agencies

If required by national law or regulation, the Investigator shall report serious adverse drug reactions suspected of being related to the studied Takeda product to the applicable regulatory authorities and IRB/EC within the timelines required by such law or regulation. The investigator shall maintain records of all such submissions.

8 Data Quality Control and Assurance

8.1 Quality Control

Takeda must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICFs (if applicable), and documentation of Institutional Review Board/Ethics Committee (IRB/EC).

Takeda shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within Takeda's systems will be periodically transferred electronically from PPD to Takeda. PPD will comply with the Takeda procedures regarding content, archiving and records management of process documents.

Procedures to ensure the accuracy and reliability of data will include the selection of qualified investigators and appropriate participating sites, and review of data collection procedures with the investigator and participating site personnel before the study.

The sponsor or sponsor representative will have a read-only to eCRF in order to assess the accuracy and completeness of the data; any discrepancies will be resolved with the investigator or designee, as appropriate.

Quality control during data collection and entry into the database will be the responsibility of the Site Responsible, who will supervise all activities regarding the study that take place in his/her Study Site. The investigator/institution will maintain all source documentation that support the data collected for each patient as well as all study documents. The investigator/institution will take measures to prevent accidental or premature destruction of these documents. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

The study will use electronic data collection, for which a set of automatic data checks with data queries will be programmed for data cleaning. Manual data monitoring will include on and off site visits and on site Source Data Verification (SDV) will include the check of the Signed Informed Consent for all subjects. Source documents (e.g., medical records, original laboratory records) and Signed Informed Consent should be available to study monitors

whenever possible, and consent to such access will be explicitly included in the Informed Consent Form.

Additional details will be specified in the Monitoring Plan.

8.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study, including the study sites, to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

8.3 Inspection by IRB/IEC or Competent Authority

Representatives from IRB/IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Takeda Brazil Research Team and must make the records available as requested.

8.4 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 finalised. 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 time frame 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.

8.4.1 Data Collection Tools and Flow

All data collected for the purpose of this study will be entered, stored and retrieved with the use of an electronic web system specifically designed for the study. The system will comprise a web-based interface for use by investigators, and a central database for storage and retrieval. The database will be physically stored at a data center designated by Takeda (CCI with appropriate measures for back-up of data and stability of the system. The system will ensure patient confidentiality, as well as security and confidentiality of the data for the duration of the study. Each Site Responsible or designee will receive from CCI a login name and a password, and will hold the responsibility for data entry into the system. Investigators will be able to access the database for the whole duration of the study. The database will contain single-choice, multiple-choice and open-field options for the entry of patient demographic and clinical data. Moreover, the system will allow for automatic data checks and the negation of queries based on programming logic.

Site Responsible will ensure source documents (institutional charts) data are attributable, accurate, complete, contemporaneous, and consistent.

The Study Site will receive data collection tools (a web system electronic data capture) from Takeda. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. Serious AE data reported in the ADR Form according to section 7 should be signed off separately by the investigator.

It is important to state that part of the data will be collect through a self-administered questionnaire using a mobile phone. In the study visit, patients will be instructed to download

the mobile application specifically developed for this study. Besides, patients will be instructed to insert in the questionnaire whenever they use Neosaldina® after an episode of TTH. After that, the mobile application will notify the patient at T0, 15', 30', 45', 1h, 1:30h, 2h to enter information regarding pain intensity and pain relief.

9 Statistical Methods and Determination of Sample Size

The statistical analysis will be performed by CCI

The Statistical Analysis Plan describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

9.1 Statistical Analysis Plan

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 6.

The main outcomes of the study are:

To describe the pain intensity of TTH subjects after the uptake of Neosaldina®.

As described in section 3.2, pain intensity being evaluated using a VAS (0 mm: no pain; 10 mm: very intense pain) at T0, 15', 30', 45', 1h, 1:30h, 2h. The score will be calculated as follows:

$$SSSSSSSS = \blacklozenge SSSSSS_{ii} \times [\Delta ttttttt_{ii}]$$

With $PIDi = P_i - P_0$ and $\Delta ttttttt_{ii}$ = time (minutes) elapsed since the previous measurement.

Descriptive analysis through tabulation of measures of central tendency and dispersion will be used for quantitative variables and frequency for qualitative variables. To compare means,

the study intends to analyze the variables with normal distribution by the Student's t-test, and those with non-normal distribution by Mann-Whitney nonparametric test. The Chi-square test will be used to assess possible differences between frequencies of categorical variables. Logistic regression will be used to build a multivariate model to assess the association between the primary outcome and exposure variables.

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.

For details of the statistical analyses please refer to the Statistical Analysis Plan.

9.2 Interim Analyses

No interim analyses are planned for this study.

9.3 Determination of Sample Size

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:

$$nn = \frac{zz_{(1-\alpha\alpha)/2}^{2}}{dd^{2}}$$

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:

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	1,70

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 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).

10 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

11 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor aims to have the results of this study published.

The Sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

Takeda may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the below essential documents in the Study Site File:

- Written agreement between the Sponsor and the Study Site Responsible;
- The study protocol and any amendments;
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible;
- Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required), including the original signed Forms;

- The list of participating subjects;
- Written IEC / IRB approval / vote according to local regulations;
- Authority approval according to local regulations;
- The completed CRFs;
- The progress reports.
- Site staff training records.
- Site staff signature delegation log.

After final database lock the Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 25 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

13 References

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