A propensity score-matched analysis of depersonalized 4-week data from the German Pain e-Registry on the efficacy and tolerability of quinine sulphate vs. pridinol mesylate in the prevention and treatment of painful nocturnal leg cramps (PRISCILA)

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Study Finalised

Administrative details

EU PAS number

EUPAS1000000105

Study ID

1000000105

DARWIN EU® study

No

Study countries

Germany

Study description

PRISCILA is an exploratory, non-interventional, post-marketing, open-label, retrospective parallel-group, comparative 4-week two-cohort-study using depersonalized data of the German Pain e-Registry (until September 30, 2023) to assess the effectiveness of the nonbenzodiazepine antispasmodic pridinol (PRI) compared to quinine sulphate (QUI) in adult patients with advanced nocturnal leg cramps (NLC) who are deemed to be in need of prescription drugs according to the mutual / shared decision of the responsible physicians and affected patients.

The primary objective of this study was the evaluation of the 4-week responder rate in comparable patient populations of the German Pain e-Registry (GPeR) with insufficient symptom relief in response to self-medication and/or non-pharmacological countermeasures for NLC who either received a prescription for QUI or alternatively with PRI.

Secondary objectives of this study focused on the overall prevalence and severity of adverse drug reactions (ADRs), ADR- and inefficiency-related treatment discontinuations in both study cohorts.
This study used depersonalized data from the German Pain e-Registry (GPeR) which is a nation-wide, web-based pain registry developed by the Institute of Neurological Sciences (IFNAP; Nuernberg) on behalf of the German Pain League (Deutsche Schmerzliga, DSL eV) to support the German Pain Association (Deutsche Gesellschaft für Schmerzmedizin, DGS eV) and its individual members to comply with the legal requirements regarding standardized documentation in pain medicine, as well as to facilitate better pain management care for people in need of it. The GPeR provides patients and physicians with standardized, fully electronic documentation aids that can be

adapted to the specifics of each individual case and that collect patient reported information on demography, history, previous and current treatment, pain characteristics and treatment response, within a daily practice setting.

Study status

Finalised

Research institutions and networks

Institutions

Institute for Neurological Sciences (IFNAP)

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Institution

Contact details

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 18/12/2023

Actual: 18/12/2023

Study start date
Planned: 02/01/2024

Actual: 02/01/2024

Data analysis start date
Planned: 14/01/2024

Actual: 14/01/2024

Date of final study report
Planned: 09/02/2024

Actual: 09/02/2024

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Study is sponsored by Strathmann GmbH & Co. KG (70%) and by O.Meany-MDPM GmbH (30%).

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Data collection methods:

Combined primary data collection and secondary use of data

Study design:

Exploratory, non-interventional, post-marketing, open-label, retrospective parallel-group, comparative 4-week two-cohort-study using depersonalized data of the German Pain e-Registry (until September 30, 2023).

Main study objective:

The primary objective of this study was the evaluation of the 4-week responder rate in comparable patient populations of the German Pain e-Registry (GPeR) with insufficient symptom relief in response to self-medication and/or non-pharmacological counter-measures for NLC who either received a prescription for quinine sulfate or alternatively with pridinol mesilate.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Quinine sulfate

Study drug International non-proprietary name (INN) or common name

PRIDINOL MESILATE

Anatomical Therapeutic Chemical (ATC) code

(M03BX03) pridinol

pridinol

Population studied

Short description of the study population

Adult Patients with a diagnosis of nocturnal leg cramps (NLC).

Patients in whom a treatment with either quinine (QUI) or pridinol (PRI) has been initiated for the first time (index date), by the current treating physicians based on individual patient needs, including (but not restricted to): decrease in functional status/activity or increase in NLC intensity, NLC duration or intolerance to or ineffectiveness of prior medications or nonpharmacological countermeasures, etc.

Patients must have a complete documentation with respect to all parameters necessary for evaluation at baseline and must have complete documentations for the full follow up period of at least 4 weeks after the first treatment index medication irrespective of the concrete duration of the index medication use.

Age groups

- **Adult and elderly population (≥18 years)**

Estimated number of subjects

1.722

Study design details

Setting

This study used depersonalized data from the German Pain e-Registry (GPeR) which is a nation-wide, web-based pain registry developed by the Institute of Neurological Sciences (IFNAP; Nuernberg) on behalf of the German Pain League (Deutsche Schmerzliga, DSL eV) to support the German Pain Association (Deutsche Gesellschaft für Schmerzmedizin, DGS eV) and its individual members to comply with the legal requirements regarding standardized documentation in pain medicine, as well as to facilitate better pain management care for people in need of it. The GPeR provides patients and

physicians with standardized, fully electronic documentation aids that can be adapted to the specifics of each individual case and that collect patient reported information on demography, history, previous and current treatment, pain characteristics and treatment response, within a daily practice setting.

The system includes scientifically validated patient questionnaires recommended by the German Pain Association, the German Chapter of the International Association for the Study of PAIN (IASP) and the German Pain League gathering information on age and sex, demographic characteristics, previous pain duration, type of pain, pain pattern, diagnosis (ICD-10), pain intensity grading according to von Korff, chronification stage according Mainz Pain Staging System, pain-related disabilities in daily life (through the modified Pain Disability Index, mPDI), physical and mental quality of life (via VR-12 PCS and MCS), the Quality-of-Life Impairment by Pain Inventory (QLIP), comorbidities and co-medication, previous and current pretreatments (pharmacological and non-pharmacological), the daily course of the pain (average, lowest and greatest 24-hour pain intensity), the individual treatment target, the average 24-hr. pain intensity index (as arithmetic mean of the 24-hour pain intensity data), as well as information on treatments and treatment-related adverse reactions, etc.

Comparators

Pharmacological treatments with quinine sulfate and pridinol mesilate for NLC followed medical requirements according to the previous decision of the participating physicians and based exclusively on individual patient needs without any external specifications.

Data sets identified for this analysis were stratified according to the drug-treatments under evaluation (cohort A: quinine sulfate - QUI; cohort B: pridinol

mesilate - PRI). As a first step, a propensity score model was developed by which treatment status (QUI vs. PRI) was regressed on distinct baseline characteristics. The estimated propensity score for a patient was the predicted probability of treatment with either QUI or PRI from the fitted regression model. Baseline characteristics included age, gender, NLC duration, number of NLC per night, weekly number of NLC, duration of individual NLC, and NLC pain intensity. Populations were matched via propensity score matching (PSM) procedures (nearest neighbor technique without replacement, caliper 0.15) and patients that were not able to be matched were excluded from further analysis. A comparison of the distribution of the baseline characteristics (especially for those data reflecting symptomatic NLC due to distinct comorbidities such as endocrine disorders, liver insufficiency, alcohol misuse, and drugs) was performed to confirm the comparability of the selected patient cohorts after PSM.

Outcomes

The proportion of patients classified as responder (as defined below) was the primary outcome variable and was compared between both evaluation cohorts (QUI and PRI).

The five criteria composing the responder composite definition were analyzed separately as well using similar methods as for the primary outcome. With exception of the treatment discontinuation rate due to ADRs or inefficiency, the responder definition of the remaining three response dimensions based on the achievement of a clinically meaningful improvement during the last 7 days of the 4-week evaluation period vs. baseline (i.e. the last 7 days before starting treatment with the index therapy).

Criteria-specific responder definitions were as follows:

- cumulative number of days/nights with NLC: proportion of patients with a

clinically relevant/meaningful decrease ≥50 percent in week 4 vs. week -1;
- cumulative number of NLC: proportion of patients with a clinically relevant/meaningful decrease ≥50 percent in week 4 vs. week -1;
- cumulative duration of NLC: proportion of patients with a clinically relevant/meaningful decrease ≥50 percent in week 4 vs. week -1;
- percentage of non-discontinuations due to ineffectiveness;
- percentage of non-discontinuations due to adverse drug reactions (DRAE).

A responder was defined as a patient who met all of the above mentioned five criteria for the last 7 days of the 4-week evaluation period after start of the index medication. Therefore, a patient that was classified as a responder had to show:
a) a positive response (defined as a 50% or even greater reduction of the cumulative number of nights with NLC, the cumulative number of NLC and the cumulative duration of NLC – each compared to the last 7 days before treatment initiation);
and
b) no discontinuation of the prescribed index medication in the 4-week follow-up period either due to ineffectiveness or as a response to an experienced ADR.

Data analysis plan

For the calculation of the primary endpoint, a sequential non-inferiority superiority analysis was performed as described below.

Non-inferiority assessment
Non-inferiority of cohort B (PRI) vs. cohort A (QUI) was confirmed if the lower bound of the 95% CI of the primary outcome response rate for cohort B was above the lower bound of the corresponding 95%-CI for cohort A.

Superiority assessment
In case non-inferiority has been confirmed, a supplemental superiority analysis has been performed if statistical analyses indicated a significant (p score < 0.05) and clinically relevant (Cohen´s d score >0.2) difference between both treatment cohorts in favor of cohort B (PRI) vs. cohort A (QUI). Superiority was rejected if a) the 95% CI of the primary outcome response rate of both treatment cohorts overlapped, and/or b) the number of reported treatment discontinuations due to drug-related adverse events (DRAEs) in cohort B (PRI) was significantly higher than those documented for cohort A (QUI).

Secondary efficacy analyses were done with respect to the absolute/relative changes of all available NLC parameters and the three efficacy response criteria of the primary endpoint at week 4 vs. week -1, and daily data reported for NLC occurrence, frequency, intensity, and duration.

Summary results

The prevalence of NLC varies across different populations and age groups. It is a common occurrence, particularly among older adults. Estimates suggest that a significant proportion of adults may experience nocturnal leg cramps at some point in their lives and the prevalence tends to increase with age.
The results of the present study PRISCILA on the effectiveness of QUI vs. PRI in a larger group of patients first of all impressively show the extent of the physical and mental impairments. Even if many people experience NLC as a singular and very temporary (and therefore harmless) event, the influence of these complaints (due to their occurrence during the night and the night-time sleep that is so important for recovery and the resulting sleep interruptions) can become clinically significant - sometimes so significant that those affected seek medical advice and help (quite contrary to the usual restraint with regard to this form of health complaint).
Both therapies proved to be safe, well-tolerated and was characterized by a

rapid and continuously increasing efficacy over the evaluation period of 4 weeks, which not only led to a highly significant reduction in all NLC-relevant parameters, but also to (mostly) highly significant improvements in NLC-related physical and mental impairments.
In a direct comparison, the direct and indirect treatment effects documented with pridinol proved to be clearer and in many cases also significantly stronger than those of quinine. These differences in many secondary endpoints are particularly noticeable in the number of patients who reached the primary endpoint defined by us for this study and who fulfilled the necessary individual requirements for it. Pridinol and the patients we evaluated not only showed a significantly stronger, but ultimately even superior effect compared to quinine, from which recommendations relevant to everyday life (e.g. for the order of sequential use) can certainly be derived.

Data management

Data sources

Data source(s)

Other data source

Data source(s), other

German Pain e-Registry

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Not applicable