Safety, tolerability, and efficacy of a dry extract from nettle leaves (Hox alpha) vs. NSAIDs in self-treatment of inflammatory joint pain in osteoarthritis. A propensity score-matched analysis of depersonalized 3-month data from the German Pain e-Registry - "Sipharo"

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Study Finalised

Administrative details

EU PAS number

EUPAS1000000564

Study ID

1000000564

DARWIN EU® study

No

Study countries

Germany

Study description

SIPHARO is an exploratory, non-interventional, post-marketing, open-label, retrospective, parallel-group, flexible-dose, comparative 12-week two-cohort study using depersonalized data from the German Pain e-Registry to evaluate the safety, tolerability, and efficacy of the nettle leaf extract Hox alpha compared to pharmacy-only nonsteroidal anti-inflammatory drugs (NSAIDs) in the self-treatment of adult patients with inflammatory joint pain in the context of osteoarthritis.

Study status

Finalised

Research institutions and networks

Institutions

O.Meany-MDPM

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Institution

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 28/06/2024

Actual: 28/06/2024

Study start date

Planned: 01/07/2024

Actual: 01/07/2024

Data analysis start date

Planned: 01/08/2024

Actual: 01/08/2024

Date of final study report

Planned: 17/12/2024

Actual: 17/12/2024

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Strathmann GmbH & Co. KG, Langenhorner Chaussee 602, 22419 Hamburg, Germany

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:

Secondary use of data

Study design:

Non-interventional retrospective dual cohort 12-week evaluation of depersonalized routine data of patients with osteoarthritis who tried to treat their pain problems with self medication (either 13-Hydroxyoctadecadienoic acid or low dose NSAIDs).

Main study objective:

Comparison of safety, tolerability and efficacy of antiinflammatory self-medication (either with low dose NSAIDs or 13-Hydroxyoctadecadienoic acid; Hox alpha) in osteoarthritis.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Hox alpha - 13-Hydroxyoctadecadienoic acid

Medical condition to be studied

Osteoarthritis

Population studied

Short description of the study population

This non-interventional retrospective evaluation used depersonalized routine/real-world data provided by the German Pain e-Registry.

This data was routinely documented using electronic devices (tablets) and the online documentation platform iDocLive® provided by O.Meany-MDPM GmbH as part of standard care and primarily for the purpose of individual patient care. At no point during the documentation process is there any intervention or financial compensation in the form of expense allowances for any additional documentation costs associated with the use of iDocLive® or for the prescription of specific therapies.

The vast majority of the data stored in the German Pain e-Registry and thus available for healthcare research is documented directly by those affected using the validated self-disclosure instruments recommended by national German pain and pain-patient associations. This gives patients the opportunity to directly provide their assessment of the effectiveness and tolerability of any therapeutic measure during the course of treatment and thus to give an unbiased account of their view of the treatment outcome (“patient-reported measure - PRM”).

Data collection using the online documentation platform iDocLive® enables a comprehensive, non-selective representation of the patient structure treated in the participating practices/institutions and their treatment data. The evaluation is based on the data of all patients documented in the German Pain e-Registry via iDocLive® within the defined evaluation period, taking into account the inclusion and exclusion criteria defined.

The selection of the pharmacotherapies used and their implementation was based on the individual needs of the respective patients, was the responsibility of the treating physician, the pharmacists involved and patients themselves, and was carried out without external influence on the basis of individualized, needs-oriented pain management in accordance with the position papers of the

German Association for Pain Medicine. The use of the electronic documentation platform iDocLive® was/is free of charge for patients, regardless of their insurance status.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Estimated number of subjects

2000

Study design details

Setting

Retrospective dual-cohort comparison of depersonalized routine/real-world data provided by the German Pain e-Registry. Inclusion criteria were: age ≥18 years, diagnosed of osteoarthritis, patients for whom treatment with Hox alpha or NSAIDs has been documented for the first time, complete documentation of all parameters required for evaluation at baseline and active use of the German Pain e-Registry for at least 12 weeks after the first dose of the index medication, regardless of the specific duration of drug therapy. Exclusion criteria were: patients with a current diagnosis of cancer, patients with another active pain condition, patients taking other pain medication.

The data sets identified for this analysis were stratified according to the drug treatments examined (cohort A: Hox alpha; cohort B: NSAIDs). In a first step, a propensity score model was developed in which treatment status (Hox alpha vs. NSAIDs) was regressed on the observed baseline characteristics. The estimated propensity score for a patient corresponded to the probability of treatment with Hox alpha or NSAID predicted by the adjusted regression model. The eight baseline characteristics used for PSM included age, sex, duration of disease, pain location, concomitant analgesic/anti-inflammatory medication, comorbidities, and concomitant non-analgesic medication (ATC, first 3 digits). The populations were matched using propensity score matching (PSM) (nearest neighbor technique without replacement, caliper 0.15; NNWOR). Patients for whom no match was possible were excluded from further analysis. A comparison of the distribution of baseline characteristics was performed to confirm the comparability of the selected patient cohorts before and after PSM.

Comparators

Hox alpha is a nettle leaf extract [(19-23:1) extraction agent 2-propanol 95% (v/v) 145 mg/hard capsule] with which 13-HOTrE (see above) can be taken in concentrated form. Hox alpha is approved as an OTC medicine for patients aged 12 years and older (approval extended in June 2003) and is available in Germany exclusively in pharmacies for the supportive treatment of rheumatic complaints and, accordingly, for the relief of muscle and joint pain. The recommended daily dose is 3 x 1 capsule after meals. The duration of use is not limited and should depend on the type, severity, and course of the disease. Low-dose NSAIDs available from pharmacies were chosen as the comparison medication.

Both drug groups can be purchased directly (over the counter) from pharmacies in Germany without a prescription and used by patients.

Outcomes

Combined safety/efficacy responder analysis: patients were classified as responders to their respective therapy if, during the 12-week evaluation phase, they a) did not discontinue treatment due to an adverse drug reaction (ADR) and at the same time b) documented clinically relevant pain relief (either ≥20 mm VAS and/or ≥30% vs. baseline) in terms of mean 24-hour pain intensity (API).

Secondary efficacy analyses were performed with regard to absolute/relative changes vs. baseline findings at the end of week 4, week 8, and week 12.

The safety and tolerability of both treatments under evaluation were assessed by summarizing and analyzing the frequency and spectrum of adverse drug reactions (ADRs), the number of patients with ADRs, and ADR-related discontinuations.

Data analysis plan

The data analyses were performed for the complete set of anonymized data provided by the Geran Pain e-Registry in accordance with specified in- and exclusion criteria and followed a modified intent-to-treat (ITT) approach, as all patient data were evaluated who (a) took/recorded at least one dose of the treatments being evaluated and (b) recorded at least one measurement after the baseline/post-dose. When changes from baseline to endpoint were evaluated, data were included in the analysis only if there was a baseline value and a corresponding post-baseline measurement. All results were summarized descriptively for the baseline value and the absolute and relative change from baseline using appropriate summary statistics and/or frequency distributions.

Safety analyses were performed based on data from all patients who received at least one dose of the drugs under investigation.

For continuous variables, descriptive statistics were summarized by the number of patients (n), mean, standard deviation (SD), 95% confidence interval (95%

CI) of the mean, median, and range (minimum - maximum). For categorical and ordinal variables, data were summarized as the number (n), percentage (%), and (where applicable) adjusted percentage (a%) of participants in each category, including 95% confidence intervals. For comparisons between groups of 2x2 contingency tables with dichotomous/binomial characteristics, the McNemar test (with Edwards correction) was used, and for categorical variables with multinomial characteristics, Pearson's chi-square tests were used. All statistical tests were performed with a two-sided significance level of 0.05. The test results were presented as specific p-values up to a level of 0.001; lower p-values were expressed as “≤0.001.” Since all comparisons beyond the primary endpoint were classified as exploratory, the significance levels were not adjusted for multiplicity.

Summary results

Identification of 1,073 data sets for patients with OA who met the inclusion/exclusion criteria [women: 58.8%; age: 68.2±11.1 (24-92) years (>80 years: 16.3%); OA in the knee/hip/shoulder/hand region: 37.7/24.7/16.7/21.0%]. With an API at BL of 54.4±14.6 (median 53, range 20-100) mm VAS, a significant reduction (p<0.001 for all vs. BL) of -18.4/-18.9 (p=0.194), -30.0/-32.3 (p<0.001) and -36.1/-40.1 (p<0.001) mm VAS after 4, 8 and 12 weeks could be observed for both treatment cohorts (NSAIDs/HOX). The proportion of patients with API relief ≥20 mm VAS vs. BL was 41.1/43.0 (p=0.382), 86.5/93.7 (p < 0.001) and 88.5/96.8% (p<0.001) after 4, 8 and 12 weeks. Overall, 502/141 patients (46.8/13.1%) documented at least 1 ADR under NSAIDs/HOX (p<0.001); 270/23 patients (25.2/ 2.1%; 53.8/16.3a%) discontinued therapy for this reason [p<0.001; OR: 11.7 (95% CI: 9.9-23.7); NNH: 4.3]. The primary endpoint was achieved under NSAIDs/HOX (n/n). after 4, 8, and 12 weeks 41.1/43.0% [p=0.382; OR: 1.1 (95% CI: 0.9-1.3); NNT 53.7], 81.8/93.3% [p<0.001; OR: 3.1 (95% CI: 2.3-4.1); NNT 8.7] and 73.2/96.2% of patients [p<0.001; OR: 9.2 (95% CI: 6.6-13.0); NNT: 4.3].

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

German Pain e-Registry

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No