Compound/Product: Diclofenac
Protocol Numbers: 300099
Reporting and Analysis plan Amendment 1, 9 June 2023

HALEON

ABBREVIATED REPORTING AND ANALYSIS PLAN

Amendment 1

A Post-hoc analysis of data obtained from China 1.16% and 2.32% study to evaluate relationship between treatment compliance and pain relief in ankle sprain patients

Protocol Studies: 300099

Phase: Phase III

Compound/Product: Diclofenac
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Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Abbreviated SAP	15-March-2023	Not applicable (N/A)
Abbreviated SAP Amendment	5-June-2023	Change in a presentation of tables. Combining Great relief and Some relief to be 2x3 contingency tables. CCI [redacted] CCI [redacted] CCI Any pain degree of relief will be considered as "Any Relief". These changes were data presentation update no change in study objectives or data from the protocol; therefore, updating only SAP was justified. 2.3 Amended Statistical Analyses section was created (pg6) to document this change: The original Pain Relief 3 categories: • Great Relief: "A Lot of Relief" or "Complete Relief" at Day 5, 12 hrs. • Some Relief: "Some Relief" or "A Little Relief" at Day 5, 12hrs. • No relief: "No Relief" at Day 5, 12hrs. Changed to the following 2 categories in the amendment. • Any Relief: "A Lot of Relief" or "Complete Relief" or "Some Relief" or "A Little Relief" at Day 5, 12 hrs. • No relief: "No Relief" at Day 5, 12hrs. Table 1-1a and 1-2a with the new categories shells were shown in Appendix (pg8)

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The purpose of this abbreviated Statistical Analysis Plan is to describe the post-hoc analysis of data obtained from China 1.16% and 2.32% study to evaluate relationship between treatment compliance and pain relief in ankle sprain patients

1.1 Background and Rationale

The results of the recently concluded study in China (Study Number 211206, entitled 'A randomized, double blind, multicenter, active-controlled, 2 treatment arm, parallel group non-inferiority study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice daily versus diclofenac diethylamine 1.16% gel applied four times daily for one week in subjects with acute ankle sprain') Chinese study have shown that after 5 days of treatment, 2 application par day, patients reach maximum pain relief. We would like to investigate the compliance data of these patients to support the recommendation to patient that patients with good compliance to treatment have pain relief after 5 days. Potential opportunity for reuse of the data to generate new claim 'Patients with good compliance to treatment have pain relief after 5 days'.

1.2 Study Designs

Phase III, randomized, double-blind, multicenter, active-controlled, 2-treatment arm, parallel group, non-inferiority study to evaluate the efficacy and safety of DDEA2.32% gel applied twice daily (BID)versus DDEA 1.16% gel applied four times daily (QID)for 1week in subjects with acute ankle sprain. To participate in the study, subjects had to have experienced an acute Grade I-II sprain of the ankle within the past 24hours and experienced pain on movement (POM) of at least 50 mm on a 100 mm visual analogue scale (VAS). Subjects were randomized as soon as possible after the injury. Subjects who met all the inclusion criteria and none of the exclusion criteria were randomized in a 1:1 ratio to 1of the 2 treatment arms.

Determination of Sample Size

Approximately 300 subjects were to be randomized to ensure at least 240 evaluable subjects completed the study for the per protocol (PP) analysis population. A maximum of 40 randomized subjects per center was considered. Approximately 120 subjects per treatment arm had been determined to provide 80% power to demonstrate non-inferiority of DDEA 2.32% gel BID with DDEA 1.16% gel QID by comparing the two-sided 95% confidence interval (CI) of the difference in mean change from baseline of VAS POM score between the 2 products with the non-inferiority margin of 13 mm.

Analysis Populations

- Enrolled population: Comprise all the subjects who had signed informed consent form (ICF), although may or may not have been randomized later into the study.
- Intent-to-treat (ITT) (randomized) population: Comprise all randomized subjects. This population was based on the treatment to which the subject was randomized. Any subject who received a treatment randomization number was considered to have been randomized.

- Safety population: Comprise all subjects who received at least 1 dose of study treatment. This population was based on the treatment the subject actually received.
- Intent-to-Treat (modified) (mITT) population: Comprise all randomized subjects who had at least 1post-baseline POM VAS assessment.
- Per protocol (PP)population: All subjects from the mITT population who did not have any major protocol deviations (PDs) (which were not affecting primary efficacy endpoint). Protocol deviations that would exclude subjects from PP population included (but were not limited to) the following:
    - Subjects failing to meet inclusion and exclusion criteria but are included in the study.
    - Subjects without a Day 5 POM VAS assessment.
    - Subjects with get application compliance ≤ 80% or weight compliance ≤ 65% or weight compliance ≥ 143% or application compliance ≥ 143% with study treatment.
    - Subjects taking prohibited medication.
    - Subjects identified with other major PDs.

1.3 Analyses Objectives

To evaluate relationship between Compliance to treatment and Pain relief after 5 days of treatment.

Potential New Claim: ‘Patients with good compliance to treatment have pain relief after 5 days’

2 Data Analysis

The statistical analysis software that will be used is SAS version 9.4 in a WINDOWS environment.

2.1 Populations for Analysis

Intent-to-Treat (ITT) population and Per protocol (PP) population will be used.

2.2 Statistical Analyses

End point:
Change from the baseline pain relief: Results from Day 5, 12 hours ±30 minutes after tube1.
Pain Relief Categories:

- Great Relief: “A Lot of Relief” or “Complete Relief” at Day 5, 12 hrs.
- Some Relief: “Some Relief” or “A Little Relief” at Day 5, 12hrs.
- No relief: “No Relief” at Day 5, 12hrs.

Compliance categories:

- Good: when > 80% of the gel has been applied and > 80% of scheduled applications made.
- Moderate: when not Good and not Poor, or Poor: when < 50% of the gel has been applied or < 50% of scheduled applications made.

Treatment arm: DDEA 2.32% Gel BID and DDEA 1.16% gel QID

Presentation of data and statistics: 3x3 contingency table (See the mock table below); Calculate frequency (n), percent (%), row percent (%) and column percent (%). No cause-effect relationship or no statistical tests will be performed.

The interpretation from the analysis will be, i.e. “xx% Patients with good compliance to treatment had at least xx% of some pain relief (or xx% of great pain relief) after 5 days".

Tables: See 3 Appendix for shell.

Table 1-1: Change from the baseline pain relief at Day 5 and compliance—ITT population

Table 1-2: Change from the baseline pain relief at Day 5 and compliance—PP population

2.3 Amended Statistical Analyses

End point:

Change from the baseline pain relief: Results from Day 5, 12 hours ±30 minutes after tube1.

Pain Relief Categories:

- Any Relief: “A Lot of Relief” or “Complete Relief” or “Some Relief” or “A Little Relief” at Day 5, 12 hrs.
- No relief: “No Relief” at Day 5, 12hrs.

Compliance categories:

- Good: when > 80% of the gel has been applied and > 80% of scheduled applications made.
- Moderate: when not Good and not Poor, or Poor: when < 50% of the gel has been applied or < 50% of scheduled applications made.

Treatment arm: DDEA 2.32% Gel BID and DDEA 1.16% gel QID

Presentation of data and statistics: 2x3 contingency table (See the mock table below); Calculate frequency (n), percent (%), row percent (%) and column percent (%). No cause-effect relationship or no statistical tests will be performed.

The interpretation from the analysis will be, i.e. “xx% Patients with good compliance to treatment had at least xx% of any pain relief after 5 days".

Tables: See 3 Appendix for shell.

Table 1-1a: Change from the baseline pain relief at Day 5 and compliance—ITT population

Table 1-2a: Change from the baseline pain relief at Day 5 and compliance—PP population

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3 Appendix

Table 1-1 Change from the baseline pain relief at Day 5 and compliance—ITT population

Treatment: DDEA 2.32% Gel BID

Table of Compliance by Pain relief				
Compliance Category	**Pain relief***			
Frequency **Percent** **Row Pct** **Col Pct**	**Great relief**	**Some relief**	**No relief**	**Total**
Good	xxx xx.xx xx.xx xx.xx	xx xx.xx xx.xx xx.xx	xx xx.xx xx.xx xx.xx	Xxx xx.xx
Moderate/Poor	x x.xx x.xx x.xx	xx x.xx x.xx x.xx	xx x.xx x.xx x.xx	Xx x.x
Total	xxx xx.xx	xx x.x	xx x.x	Xxx 100.00

*Pain relief values from Day 5, 12 hours ±30 minutes after tube1

Compliance Category:

- "Good" when > 80% of the gel has been applied and > 80% of scheduled applications made.
- "Moderate" when not Good and not Poor.
- "Poor" when < 50% of the gel has been applied or < 50% of scheduled applications made.

Pain Relief Categories:

- “Great Relief”: “A Lot of Relief” or “Complete Relief” at Day 5, 12 hrs.
- “Some Relief”: “Some Relief” or “A Little Relief” at Day 5, 12hrs.
- “No relief”: “No Relief” at Day 5, 12hrs.

Programming note: Present page-by treatment (page by DDEA 2.32% Gel BID, DDEA 1.16% gel QID and combined)

Table 1-2 Change from the baseline pain relief at Day 5 and compliance—PP population

Repeat the same Table 1-1 with PP population.

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Table 1-1a Change from the baseline pain relief at Day 5 and compliance—ITT population

Treatment: DDEA 2.32% Gel BID

Table of Compliance by Pain relief			
Compliance Category	**Pain relief***		
Frequency **Percent** **Row Pct** **Col Pct**	**Any Relief**	**No relief**	**Total**
Good	xxx xx.xx xx.xx xx.xx	xx xx.xx xx.xx xx.xx	Xxx xx.xx
Moderate/Poor	x x.xx x.xx x.xx	xx x.xx x.xx x.xx	Xx x.x
Total	xxx xx.xx	xx x.x	Xxx 100.00

*Pain relief values from Day 5, 12 hours ±30 minutes after tube1

Compliance Category:

- "Good" when > 80% of the gel has been applied and > 80% of scheduled applications made.
- "Moderate" when not Good and not Poor.
- "Poor" when < 50% of the gel has been applied or < 50% of scheduled applications made.

Pain Relief Categories:

- "Any Relief": "A Lot of Relief" or "Complete Relief" or "Some Relief" or "A Little Relief" at Day 5, 12 hrs.
- "No relief": "No Relief" at Day 5, 12hrs.

Programming note: Present page-by treatment (page by DDEA 2.32% Gel BID, DDEA 1.16% gel QID and combined)

Table 1-2a Change from the baseline pain relief at Day 5 and compliance—PP population

Repeat the same Table 1-1a with PP population.

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Related data, tables, and Listing for analysis from study 211206:

Data:

ADQS and ADEXSUM to be anonymized

Compliance:

Pain Relief: