Compound/Product: Diclofenac
Protocol Numbers: 300098
Reporting and Analysis plan, 25 April 2024

HALEON

ABBREVIATED REPORTING AND ANALYSIS PLAN
Amendment 1

A Post-hoc Analysis of Pain Relief Data Obtained from China 1.16% and 2.32% Study to Evaluate Time to Onset of Pain Relief in Ankle Sprain Patients

Protocol Studies: 300098

Phase: N/A

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Document History

Document	Version Date	Summary of Changes (New analysis or change in planned analysis)
Abbreviated RAP	25-April-2023	Not applicable (N/A)
Abbreviated RAP, Version 02	10-May-2023	Various typos; Changed sentence in Background and Rationale paragraph to, "We would like to investigate the time to relief data of these patients to support the recommendation to patients that start to relief can be attained at x hours.
Abbreviated RAP, Amendment 1	25-April-2024	Administrative change: Update phase in the front page from III to N/A Removed all comments to create clean version. Update header to be today's date (April-25-2024)

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The purpose of this abbreviated Statistical Analysis Plan is to characterize time to onset of pain relief for Voltaren 1.16 % and Voltaren 2.32 % gel in ankle sprain patients.

Background and Rationale

The results of the recently concluded study in China (Study Number 211206, entitled 'A randomized, double blind, multi-center, 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'). The Chinese study has shown that after 5 days of treatment, 2 applications per day, patients reach maximum pain relief. We would like to investigate the time to relief data of these patients to support the recommendation to patients that start to relief can be attained at x hours. This is a potential opportunity for reuse of the data to generate the new claim regarding o**nset of analgesia such as** 'Voltaren gel 1.16% /Voltaren gel 2.32% has a median time to onset of pain relief at X hours."

1.1 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 24 hours 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 2treatment 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 two 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 randomized.

- Safety population: Comprise all subjects who received at least 1dose of study treatment. This population was based on the treatment the subject 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.

1.2 Analyses Objectives

To evaluate time to onset of pain relief for Voltaren 1.16 % and Voltaren 2.32 % gel in ankle sprain patients.

Potential New Claim: 'Voltaren gel 1.16% /Voltaren gel 2.32% has a median time to onset of pain relief at X hours.'

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. Patients randomized to either Voltaren 1.16 % or 2.32 % gel will be analyzed separately and when combined into one sample.

2.2 Statistical Analyses

End point:
Spontaneous pain relief was assessed in the diary on a 5-point categorical scale:

How would you describe the relief from your ankle pain right now?"

0 = “no relief”; 1 = “a little relief”; 2 = “some relief”; 3 = “a lot of relief”; 4 = “complete relief”.
For definition of event, i.e., pain relief, a shift in one category (towards improved pain relief i.e., either 0 to 1,2,3,4 or 1 to 2,3,4 or 2 to 3,4 or 3 to 4) from baseline will be considered. Proportion of patients who achieve pain relief at each time point will be considered for analysis.

Time to onset of pain relief will be based on Survival (time to event) analysis for which pain relief data from Study Number 211206 will be considered.

Median time to event and associated 95% confidence intervals will be calculated using formulas found at PROC LIFETEST: Product-Limit Method: SAS/STAT(R) 9.2 User's Guide, Second Edition

The relevant Pain relief data is summarized in Table CCI of CSR of above-mentioned study.

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

Presentation of data and statistics: Life tables and associated Kaplan-Meier curves to estimate when at least 50% of patients achieve pain relief.

Tables and figures: See 3 Appendix for shells.

3 Appendix

Table 1-1 Time to pain relief on Day 1—ITT population, Voltaren 1.16% gel

Example of lifetable:

SurvTime		Survival	Failure	Number Failed	Number Left
0		1	0	0	27
3		0.963	0.037	1	26
7		0.9259	0.0741	2	25
8		.	.	3	24
8		0.8519	0.1481	4	23
12		0.8148	0.1852	5	22
18		0.7778	0.2222	6	21
19		0.7407	0.2593	7	20
24		0.7037	0.2963	8	19
31		0.6667	0.3333	9	18
35		0.6296	0.3704	10	17
36		0.5926	0.4074	11	16
45		0.5556	0.4444	12	15
48		0.5185	0.4815	13	14
51		0.4815	0.5185	14	13
52		0.4444	0.5556	15	12
73		0.4074	0.5926	16	11
80		0.3704	0.6296	17	10
83	*	.	.	17	9
84		0.3292	0.6708	18	8
90		0.2881	0.7119	19	7
92		0.2469	0.7531	20	6
95		0.2058	0.7942	21	5
117		0.1646	0.8354	22	4
132		0.1235	0.8765	23	3
140		0.0823	0.9177	24	2
162		0.0412	0.9588	25	1
186		0	1	26	0

Note: The marked (*) survival times are censored observations.

Summary of the Number of Censored and Uncensored Values

Stratum	Cell	Total	Failed	Censored	Percent Censored
1	adeno	27	26	1	3.70

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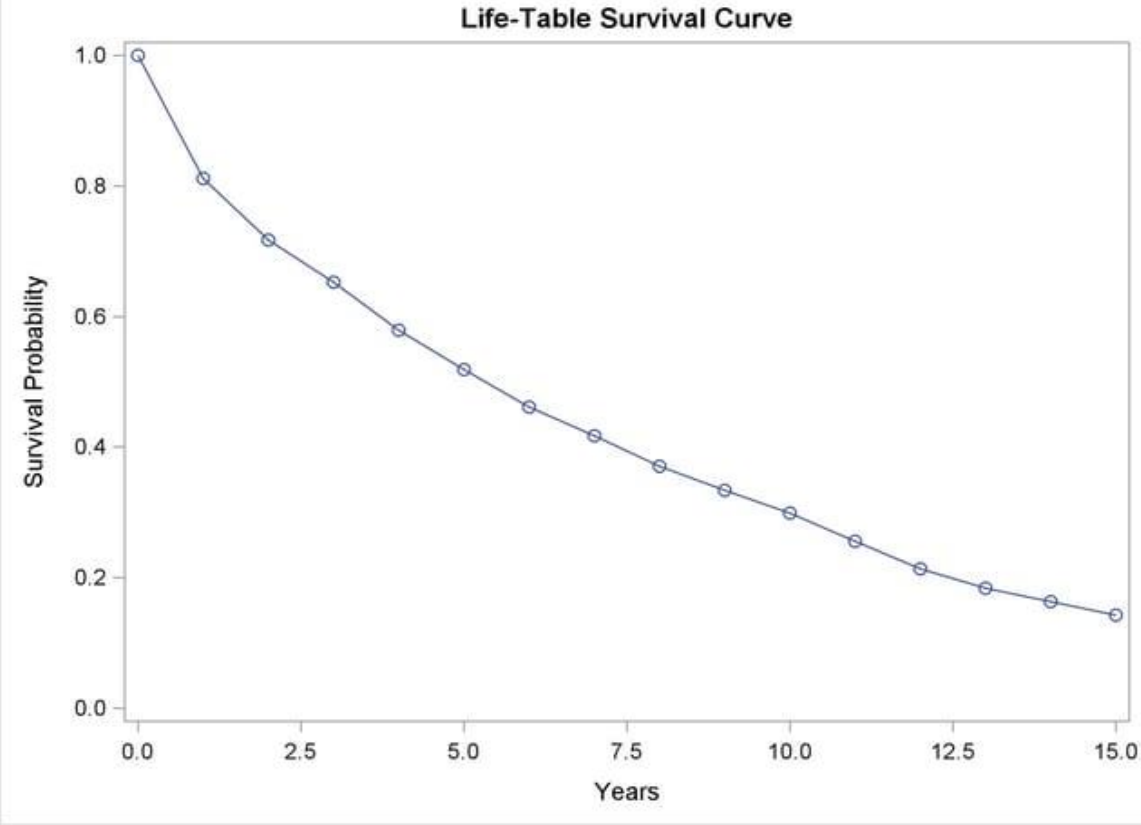
Example of survival curve



Quartile Estimates

Percent	Point Estimate	95% Confidence Interval Transform	[Lower	Upper)
75	2353	LOGLOG	2350	2358
50	1627	LOGLOG	1506	2353
25	296	LOGLOG	146	406

Mean	Standard Error
1417.21	48.14

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Programming note: Present page-by treatment.

Table 1-2 Time to pain relief on Day 1—PP population

Repeat the same Table 1-1 and figure with ITT 2.32% population.

Repeat the same Table 1-1 and figure with PP 1.16% population.

Repeat the same Table 1-1 and figure with PP 2.32% population.

Repeat the same Table 1-1 and figure with ITT combined 1.16%+2.32% population.

Repeat the same Table 1-1 and figure with PP combined 1.16%+2.32% population.

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

Data:

ADQS and ADEXSUM to be anonymized

Tables and listings of data used in the analysis:

Pain relief assessed from diary by visit and by timepoint is summarized in the ITT population in Table CCI , and in the PP population in Table CCI as well as Listing CCI Diary Selection and Subject Diary-ITT Population.