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A Prospective Real-World Evidence Study Evaluating the Effects of Voltaren Use on Mobility and Quality of Life in Subjects with Knee Osteoarthritis (OA) Pain

Protocol: 300128

EudraCT No: 2024-510839-22-00

Statistical Analysis Plan

Version 2.0

Final

05DEC2024

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This document contains confidentiality statements that are not relevant for this publicly available version

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1. Document History

Document Version	Date	Reason for changes
1.0	29OCT2024	Final version
2.0	05DEC2024	Updates from the DRM: • Section 7.1: Date of Last Study Treatment Administration updated include data collected in the End of Study Termination CRF • Section 7.1: Study day definition updated to: ○ Study Day = Date of assessment/event – Date of Baseline Visit. • Section 7.1 Baseline derivation updated in line with new study day definition. • Section 7.4.7 updated to exclude day 21 in the analysis due to Day 21 being a partial day.

2. Abbreviations

AE	Adverse Event
CI	Confidence Interval
CSR	Clinical Study Report
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ePRO	Electronic Patient reported outcome
EQ-5D-5L	EuroQol 5D Five-level version
EU	European Union
EudraCT	European Clinical Trials Database
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
KSS	Karolinska Sleepiness Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-To-Treat
MMRM	Mixed Model Repeated Measures
MVPA	Moderate and Vigorous Physical Activity
NRS	Numerical Rating Scale
OA	Osteoarthritis
PT	Preferred Term
QC	Quality control
QoL	Quality of Life
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
TOT	Total Set
WOMAC	Western Ontario and McMaster Universities Arthritis Index

3. Protocol

This study is being conducted under the sponsorship of Haleon. The clinical monitoring, data management, statistical analysis and medical writing activities are performed by CCI under contract and in collaboration with Haleon.

This Statistical Analysis Plan (SAP) provides a complete, expanded, and detailed description of the statistical methods outlined in protocol number 300128 (version 4.0, dated 8 July 2024).

All TLFs (Tables, Listings and Figures) of the final analysis, for inclusion in the CSR (Clinical Study Report) are produced by CCI

3.1 Study Objectives

The purpose of the study is to investigate how topical diclofenac use can improve functional movement, mobility and physical activity, as well as other quality-of-life parameters such as sleep, mood, and engagement in daily activities.

3.1.1 Primary Objectives

The primary objective is to evaluate the effects of Voltaren Gel on physical activity, measured through a connected activity tracker: Actigraph.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effects of Voltaren Gel on functional mobility, measured through a connected activity tracker.
- To assess the functional mobility, measured through a connected activity tracker.
- To evaluate the effects of Voltaren Gel on functional mobility, measured through subject related outcomes.
- To evaluate the effects of Voltaren Gel on pain intensity.
- To evaluate the effects of Voltaren Gel on activity-related pain and stiffness.
- To evaluate the effects of Voltaren Gel on correlates of quality of life.

3.1.3 Safety Objectives

To monitor and record adverse events (AEs) during the study period.

3.1.4 Exploratory Objectives

The exploratory objectives of the study are:

- To explore the link between Voltaren use, level of pain relief and functional mobility/quality of life.
- To evaluate time-to meaningful pain relief after Voltaren use.

3.2 Study Design

This is a prospective, open-label, single-arm, multi-country (US and EU (Poland)) real-world evidence study assessing the effects of Voltaren Gel use on functional mobility and QoL in subjects with mild/non-serious osteoarthritis (OA) of the knee.

This study will utilise a research-grade validated wearable device: Actigraph, to objectively measure changes in functional mobility, alongside subjective assessments, providing the first subject-centric data on the real-world benefits of using Voltaren Gel, beyond pain relief.

The target population comprises male and female adults aged between 40 and 85 years, diagnosed with mild/non-serious osteoarthritis of the knee and self-reported pain at the time of recruitment.

This study adopts a hybrid approach, wherein participants are only obligated to be physically present for on-site screening (Day -7), end of baseline (Day 0), and end-of-study visits (Day 21). The remaining treatment phase (Day 1-21) will be conducted in a remote manner (e.g.at home) to observe the real-world usage of the product. The study period for each subject will last a maximum of 28 days.

3.2.1 Sample Size

Sufficient individuals will be screened to enrol approximately 195 subjects assuming an estimated 25% drop out rate. It is believed that for this study 147 completed subjects are deemed sufficient to observe an improvement in QoL.

There were no previous similar studies measuring MVPA coupled with daily use of a diclofenac gel. Thus, the effect size was chosen based on literature review to detect even mild improvement in QoL factors: "An effect magnitude between 0.2 and 0.5 indicates mild improvement, between 0.5 and 0.8 indicates moderate improvement, and greater than 0.8 indicates considerable improvement in symptoms and QoL." The sample size was based on a significance level (α) = 0.05, Power (1-β) = 80%, and a standardized effect size of 0.25

Literature review also indicated that QoL scores are not normally distributed. Subjects with worse baseline symptoms showed larger improvement in QoL scores. Therefore, a two-sided non-parametric Wilcoxon Signed Rank test calculation was performed.

Using the above parameters, we obtain a sample size N =195 to retain the required 147 completed subjects. Therefore, it has been determined that 195 eligible subjects will be recruited for the trial, with an anticipated 147 study subjects expected to successfully complete the study.

3.3 Study Schedule

Table 1: Schedule of Events

Procedure/Assessment	Screening and Enrolment	Baseline *	Study Treatment Phase **						
	Day -7 (Visit 1)	D-7 to D0 (Visit 2)	D1	D1 to D6	D7	D8 to D13	D14	D15 to D20	D21 (Visit 3)
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Demographics	X								
Current/Prior concomitant medication review	X	X	X	X	X	X	X	X	X
Subject Eligibility	X								
Study Product use			X	X	X	X	X	X	X
Urine Pregnancy Test***	X								X

Procedure/Assessment	Screening and Enrolment	Baseline *	Study Treatment Phase **						
	Day -7 (Visit 1)	D-7 to D0 (Visit 2)	D1	D1 to D6	D7	D8 to D13	D14	D15 to D20	D21 (Visit 3)
Dispensing of (Actigraph) [a]	X								
Dispensing of Product (Voltaren) [a]		X							
Pain									
Numeric Rating Scale [b]	X	X	X	X	X	X	X	X	X
Visual Analogue Scale [b]	X	X							
Western Ontario and McMaster University Osteoarthritis index (WOMAC) Pain Subscale [b]		X	X		X		X		X
Mobility									
Tracker-derived mobility assessment [c]		X	X	X	X	X	X	X	X
Western Ontario and McMaster University Osteoarthritis index (WOMAC) Stiffness Subscale [b]		X	X		X		X		X
Western Ontario and McMaster University Osteoarthritis index (WOMAC) Function Subscale [b]		X	X		X		X		X
Sleep									
Tracker-derived sleep assessment		X	X	X	X	X	X	X	X
Karolinska Sleepiness Scale [b]		X	X	X	X	X	X	X	X
Quality of Life									
EQ-5D-5L Quality of Life Questionnaire		X	X		X		X		X
Safety									
Adverse Events (AEs) Review [c]	X	X	X	X	X	X	X	X	X
Study Conclusion									
Returning Actigraph device and the allocated product									X
End of Study Questionnaires									X

a. Actigraph tracker is dispensed at screening visit post consent of patient during enrolment for the study (D -7 – Visit 1) and Voltaren is dispensed immediately post eligibility of the subject at the end of Baseline period (Day 0 – Visit 2).

b. The questionnaires such as: Pain Visual Analogue Scale (VAS) / Numeric Rating Scale (NRS), will initially be performed on site during enrolment period (Visit 1) and prior to dispensing of Voltaren (Visit 2), to complete the baseline assessment. Subjects are then required to perform the assessment of NRS, Western Ontario and McMaster University Osteoarthritis index (WOMAC), Karolinska Sleepiness Scale and the EQ-5D-5L Health questionnaire at site prior to dispensing of Voltaren (Day 0 – Visit 2) and then at home during the study period and report the score within the eDiary.

c. Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

* Baseline period will be flexible and last a minimum of 3 days and maximum 7 days to collect sufficient baseline information from study subjects. When pain levels reach ≥40 mm ≤ 70mm in the VAS/NRS scale, the day before starting the use of Voltaren, study subjects will be prompted to answer relevant questionnaires to assess baseline levels. Site staff to monitor subjects eDiary and dispense Voltaren when patients have ended baseline period. Subjects can also notify site staff when their baseline period has ended to commence the study.

** Study period will last a maximum of 28 days. Study subjects are allowed to stop using Voltaren if they feel that their pain has successfully resolved and do not need to use the product anymore.

***Urine test only needed for women of childbearing potential and postmenopausal women who are not surgically sterile. Urine samples are collected to detect the presence of human chorionic gonadotropin (hCG), a hormone produced during pregnancy.

3.4 Interim Analyses

No interim analyses are planned.

3.5 Changes in the Conduct of Study or Planned Analysis compared to protocol

Protocol Version Final 4.0 dated 08JUL2024 states in Section 13.2 on page 55 that:

> "The modified Intent-To-Treat (mITT) population will include all subjects who use study product at least once and have data from at least one post baseline QoL questionnaire to support at least one of the secondary endpoint assessments. QoL and ePRO data will be summarized using the mITT population only".
>
> This has been updated in the SAP to include that subjects must meet the inclusion/exclusion criteria to be included in the mITT as below:
>
> "The modified Intent-To-Treat (mITT) population will include all subjects who meet the inclusion/exclusion criteria, who use study product at least once and have data from at least one post baseline QoL questionnaire to support at least one of the secondary endpoint assessments (i.e. have a non-missing response in the 'Western Ontario and McMaster University Osteoarthritis Index' or 'EQ-5D-5L Quality of Life Questionnaire' eDiary pages). The mITT population will be used for all efficacy analysis."

4. General Definitions

4.1 Report Language

The output of the analyses (tables, figures, listings, and inferential analyses) is prepared in English.

4.2 Analysis Software

The statistical analysis is performed using the SAS® statistical software package (Statistical Analysis System, Version 9.4 or later).

5. Data Preparation

5.1 Data Handling and Medical Coding

For data quality control, medical coding and data provided by third parties which is not contained in the clinical database (e.g. pharmacokinetic data, central reader data), please refer to the Data Management Plan (version 1.0, dated 11APR2024 or higher including the Data Validation Plan (version 3.0. dated 03JUL2024) or higher. The adverse event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, Version, 26.0 (Mar 2023) (or higher).

5.2 CDISC

All output as defined in the SAP are generated based on CDISC ADaM datasets, as per contract with Haleon. Specifications for the ADaM datasets (as well as SDTM datasets) are described in a separate document.

5.3 SAS-Programming Quality Level

The following quality level of programming deliverables is applied, as per contract with Haleon:

All statistical output receives a tailored Quality Control (QC) approach by:

Table 2: SAS-Programming Quality Level

DELIVERABLE	DOUBLE PROGRAMMING?
CDISC SDTM datasets	
Including QC against the applicable CDISC guidelines.	YES
CDISC ADaM datasets	
Including QC against the SAP and applicable CDISC guidelines.	YES
Derived datasets	YES
Tables and Figures	YES
Inferential analyses	YES
Data Listings	
Listings	NO
Listings for Data Review Meeting that do not need complex selection	NO
Listings for Data Review Meeting that do need complex selection*	YES
* The selection of the data is double programmed from the source dataset.	

All TLFs undergo the following by the Quality Control (QC) team:

- Comparison with specifications (i.e., SAP and shells)
- Cross checking with other TLFs for consistency and correctness
- Sensibility review
- SAS log review

In addition, a Senior Review is also performed by a reviewer independent of the study team. The reviewer studies all tables, listings and graphs for consistency and correctness.

All TLFs undergo comparison with specification (i.e. SAP and templates), cross checking with other TLFs for consistency and correctness, a sensibility review, and SAS log review by the Lead Statistical Programmer or Lead Statistician.

6. Analysis Populations and Subgroups

6.1 Analysis Populations

Total Set (TOT)

The Total Set consists of all subjects who provided informed consent on the 'Informed Consent' Electronic Case Report form (eCRF) page.

Enrolled Population

The enrolled population will include all subjects who meet the inclusion/exclusion criteria as recorded on the 'Subject Eligibility: Inclusion/Exclusion Criteria' eCRF page.

Screening Failures

Screening Failures are defined as subjects who provided informed consent but failed to meet all inclusion criteria and/or met at least one exclusion criteria, as recorded on the 'Subject Eligibility: Inclusion/Exclusion Criteria' eCRF page.

Safety Population (SAF)

The safety population will include all subjects who use study product at least once i.e. if a subject has a date of first study treatment administration as described in section 7.1. The safety population will be used for safety variables.

Modified Intent-To-Treat (mITT) population

The modified Intent-To-Treat (mITT) population will include all subjects who meet the inclusion/exclusion criteria, who use study product at least once and have data from at least one post baseline QoL questionnaire to support at least one of the secondary endpoint assessments (i.e. have a non-missing response in the 'Western Ontario and McMaster University Osteoarthritis Index' or 'EQ-5D-5L Quality of Life Questionnaire' eDiary pages). The mITT population will be used for all efficacy analysis.

6.2 Subgroup Definitions

No subgroup analysis is planned.

7. Definition of Time Points and Analysis Variables

7.1 Definition of Time Points

Visits are labelled in all TLF outputs as they were entered into the eCRF/eDiary without re-labelling. External data will be analysed according to the study day calculated.

Table 3: Study Visits

Scheduled Visit	Scheduled Visit Label	Scheduled Study Day
Screening*	Screening	-7
Day -6	Day -6	-6
…	…	…
Day -1	Day -1	-1
Day 0*	Day 0	0

Scheduled Visit	Scheduled Visit Label	Scheduled Study Day
Day 1	Day 1	1
Day 2	Day 2	2
Day 3	Day 3	3
Day 4	Day 4	4
Day 5	Day 5	5
…	…	…
Day 21*	Day 21	21

*Indicates mandatory site visit.

Date of First Study Treatment Administration

Date of first study treatment administration is derived as:

- (The earliest recorded date where the answer to the question "Did you use yesterday the Voltaren Gel as per label and leaflet instructions?" is "Yes" on the 'Study Product Use' eDiary page) - 1.

Date of Last Study Treatment Administration

Date of last study treatment administration is defined as:

- "Date of last application of study drug" as recorded in the 'Study Termination' eCRF page.).

Study Day

The study day of events/assessments is calculated as:

- Study Day = (Date of assessment/event - Date of Baseline Visit).

Baseline

The baseline value for QOL data is defined as measurements collected on Day 0.

Baseline for data collected through connected activity tracker is derived as an average per day:

- Sum of the variable of interest/baseline period.

Where the baseline period is the number of non-missing days between day -6 to day 0 – Prior to product usage.

7.2 Event Dates

Medical events are defined as medical history, prior and concomitant medication, non-drug therapy and procedures, and adverse events.

7.2.1 Event Days

All types of events have a Start/Onset Day calculated and, if not 'Ongoing', have a Stop/Resolution Day calculated equivalent to Study Day as defined in 7.1.

7.2.2 Missing Dates and/or Times

Missing and/or incomplete dates/times for events are imputed for calculating Start Day and End Day only. Dates are listed as missing/incomplete [with "-" replacing missing information]

but the Start/End Day/Time are listed between square brackets to denote it is calculated based on missing data (i.e. [-28], [1], [Ongoing]).

Missing and/or incomplete dates/times are imputed in a manner that assumes the worst-case scenario (i.e., Start as close as possible to the First Study Treatment Administration and stopped such that it is assumed to have lasted for the longest possible duration, considering that the Start date/time should not be after the Stop date/time).

Technically, this is done as follows for End Day/Time:

- For a completely missing stop year (regardless of minute, hour, day, or month response) the event is assumed to be ongoing.
- For a missing stop hour (and the event is not 'Ongoing'):
  - it is assumed to have ended on hour 23 (11pm) of that day
- For a missing stop minute (and the event is not 'Ongoing'):
  - it is assumed to have ended 59 minutes past the hour
- For a missing end day (and the event is not 'Ongoing'):
  - it is assumed to have ended on the last day of the month, if the month is given
  - it is assumed to have ended on the 31st of December of that year, if the month is also missing

Technically, this is done as follows for Start Day/Time:

- For a completely missing Start date (day, month, and year regardless of the minute and hour recorded)
  - the Start Day of the event is "[Pre-Treat]" if the end date or partial end date concludes the event stopped before First Study Treatment Administration (i.e. assumed to be prior or pre-treatment as is applicable).
  - in all other instances (i.e. inconclusive end date or Ongoing event) the Start Day of the event is assumed to be the same date and time as First Study Treatment Administration (i.e. assumed to be concomitant or treatment emergent as applicable.)
- For a missing start hour:
  - it is assumed to have started on hour 00 (midnight) of that day.
  - or at the time (hour and minute) of First Study Treatment Administration if the start date (day, month and year) is the same as the First Study Treatment Administration date.
- For a missing start minute:
  - it is assumed to have started on minute 00 of that hour.
  - or at the time (hour and minute) of First Study Treatment Administration if the start date (day, month and year) is the same as the First Study Treatment Administration date.
- For a missing Start day but given month:
  - it is assumed to have started on the first day of the month.
  - or at the date of First Study Treatment Administration if the start month and the year is the same as the First Study Treatment Administration month and year.
- For a missing start month:
  - it is assumed to have started on the first of January of that year.
  - or at the date of First Study Treatment Administration if the start year is the same as the First Study Treatment Administration year.

7.3 Study Treatments

'Table 4: Study Treatments' shows the Study Treatments and how they are labelled in all Listing outputs. The study treatment assigned at baseline is used.

Table 4: Study Treatments

Study Treatment	Study Treatment Label
Voltaren Gel 1% (diclofenac sodium)	Voltaren Gel 1%
Voltaren Gel 1.16% (diclofenac diethylammonium)	Voltaren Gel 1.16%
Voltaren Gel 2.32% (diclofenac diethylammonium)	Voltaren Gel 2.32%

7.4 Analysis Variables

7.4.1 Disposition

Subject disposition data are collected on the 'Study Termination' eCRF page. Subjects are recorded as "Completed", "Screening failure", or "Early withdrawal". The date of the disposition event, date of last application of study drug and, if applicable, the date of death is recorded.

If applicable, the primary reason for discontinuation may include any of the following:

- Adverse Event (with a drop down to specify the AE number);
- Death;
- Inclusion not met/ Exclusion criteria met;
- Lack of efficacy;
- Lost to follow-up;
- Non-compliance with study drug;
- Occurrence of pregnancy;
- Physician's decision;
- Protocol violation;
- Withdrawal of consent;
- Withdrawal due to no pain;
- Other (with a free text to specify).

7.4.2 Demographic and Other Baseline Characteristics

Demographic data (Month and Year of Birth, Age, Sex, Race and Ethnicity) are recorded on the 'Demographics' eCRF page.

Age

Age (years) is manually entered into the eCRF.

Sex

Sex is recorded as "Male" or "Female".

Race

Race is recorded as "American Indian or Alaska Native", "Asian", "Native Hawaiian or Other Pacific Islander", "Black or African American", "White", "Unknown", "Not reported", or "Other (please specify)". More than one race may be selected.

Ethnicity

Race is recorded as "Hispanic or Latino", "Not Hispanic or Latino", "Not reported" or "Unknown".

VAS

VAS score is recorded on the 'Visual Analogue Scale' eCRF page at screening and baseline.

Corrections to the scores are applied for scores recorded on or before 08JUL2024 due to the incorrect length of scale used in performing the test. This is documented in non-conformity number 61/2024.The following corrections are applied:

- For site CCI VAS score = raw VAS score x 0.82.
  - Correction factor calculated as: 100 ÷ 122 (actual length of scale)
- For site CCI VAS score = raw VAS score x 0.88.
  - Correction factor calculated as: 100 ÷ 113 (actual length of scale)

7.4.3 Medical/Surgical History and Concomitant Diseases

Relevant medical/surgical conditions, in the last year, including allergies or drug sensitivity, are recorded at the Screening visit on the 'Medical History' eCRF page.

The following variables are collected:

- Whether or not there are any medical/surgical conditions.
- For each condition: the event number (automatically prefilled), the reported term, the start date and, if applicable, the end date. If a condition is ongoing this is also recorded.

For each condition, not ongoing, the duration (days) is computed as: [(Stop date – Start date) +1].

Knee osteoarthritis diagnosis is recorded at the screening visit on the 'Knee Osteoarthritis Diagnosis' eCRF page.

The following variables are collected:

- Date of first diagnosis
- Whether the knee pain is affecting both knees (bilateral) or just one knee (unilateral)

Time since first diagnosis is computed as: Informed Consent Date - Date of First Diagnosis.

7.4.4 Prior and Concomitant Medication

Prior and Concomitant medication data are collected throughout the study on the 'Prior and Concomitant Medications' eCRF page. For each medication, the number (automatically prefilled), the trade or generic name is recorded with the following variables.

Route

The route of administration is recorded as "Intralesional", "Intramuscular", "Intraocular", "Intraperitoneal", "Intravenous", "Nasal", "Oral", "Rectal", "Respiratory (inhalation)", "Subcutaneous", "Topical", "Transdermal", "Vaginal", or "Other (please specify)" .

Dose

The dose of administration is recorded with the dose unit.

Frequency

The frequency of administration is recorded as "Once", "Daily", "2 Times per day", "3 Times per day", "4 Times per day", "Every other day", "1 Time per week", "2 Times per week", "Every month", "As needed", "Unknown", or "Other (please specify)" .

Indication

The indication for the medication is recorded as "Adverse Event", "Medical History", "Procedure", or "Other (please specify)". If the indication is not "Other", then the related Adverse Event, Medical History or Procedure is recorded.

Start/End Date, Time, and Day

The start, end date and time is recorded. If the medication is ongoing this is recorded.

All medications have a start day and end day calculated as described in Section 7.2.

'Prior medications' are medications that were stopped before First Study Treatment Administration (end day < 1).

'Concomitant medications' are medications that were stopped on or after First Study Treatment Administration (end day ≥ 1 or are ongoing). These may have started at any time (i.e. prior to, on, or after, date of First Study Treatment Administration).

7.4.5 Concomitant Procedures

Concomitant procedures are recorded on the 'Concomitant Procedures' eCRF page. The procedure name, start date, end date (or ongoing), and indication ("Adverse Event", "Medical History", or "Other (please specify)") is recorded. If the indication is "Adverse Event" or "Medical History" the related Adverse Event or Medical History is recorded.

7.4.6 Treatment Compliance and Exposure

Total Number of Days on Study

Total Number of Days on Study is calculated as:

- Total Number of Days on Study = (Date of Study Completion / Discontinuation - Date of Screening Visit) +1.

Total Number of Days in Treatment Phase

Total Number of Days in Treatment Phase is calculated as:

- Total Number of Days Treatment Phase = (Date of Study Completion / Discontinuation - Date of Baseline Visit)+1.

Duration of Exposure

Duration of exposure is calculated as:

- Duration of exposure (days) = (Date of Last Study Treatment Administration - Date of First Study Treatment Administration) + 1

Study Treatment Compliance

Study treatment compliance is determined from the 'Study Product Use' eDiary pages and calculated as:

- Treatment compliance (%) = (Number of days the answer to "Did you use yesterday the Voltaren Gel as per label and leaflet instructions?" is "Yes" ÷ Duration of exposure) * 100.

Actigraph Device Compliance

The required Actigraph daily minimum wear time is 20 hours. Daily wear minutes is collected via the Actigraph device and converted to hours as:

- Daily wear time (hours) = Daily wear minutes ÷ 60.

Actigraph device compliance is calculated as:

- Actigraph device compliance (%) = (Number of days the daily wear time (hours) is greater than or equal to 20 hours ÷ Total number of days on study) * 100

Awake Trigger Compliance

Awake trigger compliance is determined from the 'Study Product Use' eDiary pages and calculated as:

- Awake trigger compliance (%) = (Number of days the answer to "Did you click the event trigger at awake yesterday?" is "Yes" ÷ Total Number of Days in Treatment Phase) * 100.

Bedtime Trigger Compliance

Bedtime trigger compliance is determined from the 'Study Product Use' eDiary pages and calculated as:

- Bedtime trigger compliance (%) = (Number of days the answer to "Did you click the event trigger at bedtime yesterday?" is "Yes" ÷ Total Number of Days in Treatment Phase) * 100.

7.4.7 Efficacy Variables

7.4.7.1 Primary Efficacy Variable

For primary analysis, average minutes of MVPA on Day 7 will be calculated over all non-missing days between study day 1 (product usage) through 7, inclusive and it is collected via the Actigraph device. Average minutes of MVPA on Day 14 will be calculated over all non-missing days between study day 8 through 14, inclusive. Average minutes of MVPA on Day 21 will be calculated over all non-missing days between study day 15 through 20, inclusive. Any days beyond day 20 will be excluded from all summaries and analyses and will only be present in listed data.

Average baseline MVPA is computed as:

- Average baseline MVPA = total minutes of MVPA over the baseline period / number of days with non-missing data over the baseline period.
    - Baseline period is defined in section 7.1.

Average MVPA for each 7-day period is calculated as:

- Average MVPA for 7-day period = total minutes of MVPA over the period / number of days with non missing data over the period.
    - If every day within the 7 – day period has non missing data, then the Average MVPA for 7- day period will be computed as: total minutes of MVPA over the period / 7.

Change from baseline is calculated as:

- Average MVPA for 7-day period - Average baseline MVPA.

7.4.7.2 Secondary Efficacy Variables

Change from baseline on Days 7, 14, and 21 in Daily Average number of steps taken

Average baseline number of steps taken is calculated as:

- Average baseline number of steps taken = total number of steps taken over the baseline period / number of days with non missing data over the baseline period.
    - Baseline period is defined in section 7.1.

Daily average number of steps taken for each 7-day period is calculated as:

- Daily average number of steps taken for 7-day period = total number of steps over the period / number of days with non missing data over the period.

Change from baseline is calculated as:

- Daily average number of steps taken for 7-day period - Average baseline number of steps taken.

Change from baseline on Days 7, 14, and 21 in Ratio of sedentary/non-sedentary time

Number of sedentary behaviour minutes in the day is defined as Sedentary Activity from the Day Level Activity Outcomes.

Number of non-sedentary behaviour minutes in the day is derived as:

- Sum of Light Activity and MVPA from the Day Level Activity Outcomes.

Ratio of sedentary/non-sedentary time per day is calculated as:

- Ratio of sedentary/non-sedentary time per day = Number of minutes in the day defined as Sedentary behaviour ÷ Number of minutes in the day defined as Non-Sedentary behaviour.

Baseline ratio of sedentary/non-sedentary time is calculated as described in section 7.1, where the variable of interest is the ratio of sedentary/non-sedentary time.

Ratio of sedentary/non-sedentary time for each 7-day period is calculated as:

- Ratio of sedentary/non-sedentary time for 7-day period = Total number of minutes defined as Sedentary behaviour in the 7-day period/ Total number of non-sedentary behaviour minutes in the 7-day period

Change from baseline is calculated as:

- Ratio of sedentary/non-sedentary time for 7-day period - Baseline ratio of sedentary/non-sedentary time.

Change from baseline on Days 7, 14, and 21 in Gait, assessed through speed and step irregularity (measured via cadence and gait speed)

Average baseline cadence is calculated as:

- Average baseline cadence = total mean cadence over the baseline period / number of days with non-missing data over the baseline period.
    - Baseline period is defined in section 7.1.

Average cadence for each 7-day period is calculated as:

- Average cadence for 7-day period = total mean cadence / number of days with non missing data over the period.

Change from baseline is calculated as:

- Average cadence for 7-day period - Average baseline cadence.

Average baseline gait speed is calculated as:

- Average baseline gait speed = total mean gait speed over the baseline period / number of days with non-missing data over the baseline period.
    - Baseline period is defined in section 7.1.

Average gait speed for each 7-day period is calculated as:

- Average gait speed for 7-day period = total mean gait speed / number of days with non missing data over the period.

Change from baseline is calculated as:

- Average gait speed for 7-day period - Average baseline gait speed.

Change from baseline on Days 7, 14, and 21 in Indices of morning stiffness (assessed through levels of mobility 30- and 60-mins post-wake)

30 minutes post-wake is defined as the interval from bed interval end date/time from the Sleep Metrics by Night Outcome + 30 minutes.

Daily morning stiffness 30 minutes post-wake is defined as the total vector magnitude counts 30 minutes post-wake.

Average baseline morning stiffness 30 minutes post-wake is calculated as:

- Average baseline morning stiffness 30 minutes post-wake = total Daily morning stiffness 30 minutes post-wake over the baseline period / number of days with non-missing data over the baseline period.
    - Baseline period is defined in section 7.1.

Average morning stiffness 30 minutes post-wake for each 7-day period is calculated as:

- Average morning stiffness 30 minutes post-wake for 7-day period = total Daily morning stiffness 30 minutes post-wake / number of days with non missing data.

Change from baseline is calculated as:

- Average morning stiffness 30 minutes post-wake for 7-day period - Average baseline morning stiffness 30 minutes post-wake.

60 minutes post-wake is defined as the interval from bed interval end date/time from the Sleep Metrics by Night Outcome + 60 minutes. Daily morning stiffness 60 minutes post-wake, average baseline morning stiffness 60 minutes post-wake, average morning stiffness 60 minutes post-wake for each 7-day period and change from baseline are calculated in the same way as described for 30 minutes post-wake.

MVPA on each day of the study (Baseline to final treatment day 21)

The variable used is the total number of minutes of MVPA calculated for each study day.

Change from baseline in self-reported pain intensity, assessed through Numeric Rating Scale (NRS) (daily assessment).

Self-reported pain intensity is recorded on the 'Numeric Rating Scale' eDiary page at each scheduled timepoint.

Baseline is the value collected on Day 0, as described in section 7.1.

Change from baseline is calculated as:

- NRS score at Scheduled Timepoint – NRS baseline score (Day 0)

WOMAC Subscale Score (Pain WOMAC A, Stiffness WOMAC B and Function WOMAC C)

The WOMAC® LK3.0 is composed of 3 subscales (A: Pain, B: Stiffness, C: Physical Function). There are 5 components for subscale A (Pain), 2 components for subscale B (Stiffness), and 17 components for subscale C (Physical Function) each component is measured on a 0-4 scale [1].

A WOMAC subscale score is calculated, at Day 0, Day 1, Day 7, Day 14 and Day 21, as the sum of the available component scores within the subscale. For convenience this is normalized on a 0-100 scale by dividing the sum appropriately:

- Pain WOMAC A = (sum of raw score items in dimension) x 5
- Stiffness WOMAC B= (sum of raw score items in dimension) x 12.5
- Function WOMAC C = (sum of raw score items in dimension) x 1.47

The subscale score will be set to missing according to the following:

- if ≥ 2 Pain components are missing
- if both Stiffness components are missing
- if ≥ 4 Physical Function components are missing

As outlined in the WOMAC scoring guide [1], if there are missing components within a subscale but the number of missing components does not meet the criteria for setting the subscale score to missing, then the value of the missing components will be set equal to the mean of the available components of the respective subscale.

WOMAC subscale scores and normalized subscale scores are calculated, as described in the previous section, for baseline (Day 0) and for all post baseline timepoints: Day 1, Day 7, Day 14 and Day 21.

Normalized WOMAC subscale scores are used for the following endpoints:

- Change from baseline in WOMAC Physical Function subscale on Days 7, 14, and 21
- Change from baseline in the WOMAC subscales, Pain (composite) and Stiffness (composite) on Days 7, 14, and 21

For each scheduled time point:

- Baseline is the value collected on Day 0, as described in section 7.1.
- Change from baseline is calculated as:
- Normalized WOMAC subscale score at Scheduled Timepoint – Normalized WOMAC subscale baseline score (Day 0)

WOMAC Global Score

The total WOMAC® LK3.0 global score, calculated at, Day 0, Day 1, Day 7, Day 14 and Day 21, is computed as the sum of the 3 normalized WOMAC subscale scores.

The total WOMAC score will be set to missing if any of the WOMAC subscale scores are set to missing as defined above. The WOMAC global score is:

WOMAC Global Score = WOMAC A + WOMAC B + WOMAC C

WOMAC Global Score and change from Baseline is calculated at all visits.

Change from baseline in Karolinska Sleepiness Scale on Days 7, 14, and 21

KSS is recorded on the 'Karolinska Sleepiness Scale' eDiary page at each scheduled timepoint. Change from baseline is calculated as:

- KSS at Scheduled Timepoint – KSS at Day 0

EQ-5D-5L

Health-related quality of life is recorded on the 'EQ-5D-5L Quality of Life Questionnaire' eDiary page.

The EQ-5D is a standardized instrument for assessing health-related QoL, which provides a simple descriptive profile and a single index value for health status in a variety of health conditions. The EQ-5D includes single item measures of five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The EQ-5D-5L includes five levels of severity (i.e., no problems, slight problems, moderate problems, severe problems, and extreme problems) for each of the five EQ-5D dimensions. These levels are scored from 1=no problems to 5= extreme problems. (EuroQol Research Foundation, 2019).

EQ-5D-5L Health State

The scores (1-5) for the five dimensions are concatenated into a 5-digit code (in the order mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that describes the patient's health state.

EQ-5D-5L Index

From the EQ-5D-5L health state the EQ-5D-5L index values are calculated based on the Crosswalk Value Set for the US. If one of the dimensions has a missing score, the EQ-5D-5L index value is derived as missing.

EQ-5D-5L index values are used for the following endpoint:

- Change from baseline in Health-related quality of life, EQ-5D-5L, on Days 7, 14, and 21.

7.4.7.3 Exploratory Variables

Elapsed time from Voltaren Gel use to achieving time to meaningful pain relief to end of study

Date of meaningful pain relief is defined as the earliest date where:

- The answer to "Did you use yesterday the Voltaren Gel as per label and leaflet instructions?" is "No"
  AND
- The answer to "If No, please specify the reason:" is "No pain anymore"

On the 'Study Product Use' eDiary page.

The time to event is derived in days as:

- Date of event/censoring – date of First Treatment Administration +1

Date of First Treatment Administration is derived as explained in section 7.1.

For patients who complete or discontinue the study without event occurrence, the patients are considered "censored" and the date of censoring is the date of study discontinuation recorded on the 'Study Termination' eCRF page.

7.4.8 Safety Variables

Adverse Events

An adverse event (AE) is defined as "any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device)".

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

AE data are collected from the time that informed consent was given for the duration of the trial on the 'Adverse Events' eCRF page.

The following information is recorded:

- AE term;
- Start date/time;
- End date/time (or ongoing);
- Severity ("Mild", "Moderate", or "Severe");
- Serious ("Yes", "No")
    - if AE is serious;
        - Death ('No', 'Yes') if yes then also date of death;
        - Life threatening ('No', 'Yes');
        - Hospitalization ('No', 'Yes') if yes then also start and end date;
        - Significant Disability ('No', 'Yes');
        - Congenital Anomaly or Birth Defect ('No', 'Yes');
        - Other Medically important event ('No', 'Yes');
- Outcome ("Fatal", "Not recovered/ not resolved", "Recovered/ resolved", "Recovered with sequelae / resolved with sequelae", "Recovering / resolving", or "Unknown");
- Relationship to study drug ("Unknown", "Not Related", "Unlikely", "Possible", "Probable", or "Definite");
- Action taken with study treatment ("Dose not changed", "Dose increased", "Dose rate reduced", "Dose reduced", "Drug interrupted", "Drug withdrawn", "Not applicable", or "Unknown");
- Other action taken:
    - None ('No', 'Yes');
    - Medication prescribed ('No', 'Yes');
    - Device removed ('No', 'Yes');
    - Surgery ('No', 'Yes');
    - Other ('No', 'Yes');

Pre-Treatment Adverse Events

Pre-treatment AEs are defined as AEs that started during the pre-treatment period (date of informed consent up to the date/time of first study treatment administration).

Serious AE

A Serious AE is any AE where the 'Serious' flag has been marked as 'Yes'.

Serious AEs have the following additional information recorded: did AE result in death, was AE life threatening, did AE result in initial or prolonged hospitalization, did AE result in disability or permanent damage, was AE associated with a congenital anomaly or birth defect, and was AE a medically important event not covered by other serious criteria.

Treatment-Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the date of the first study treatment administration and is derived using start/onset and stop dates only.

Missing AE dates are handled according to the same rules as specified for concomitant medications in Section 7.2.

Serious Treatment-Emergent Adverse Event (Serious TEAE)

A Serious TEAE is any TEAE where the 'Serious' flag has been marked as 'Yes'.

TEAE Leading to Permanent Withdrawal of Study Treatment

A TEAE leading to permanent withdrawal of the Study Treatment is defined as a TEAE where the action taken with study treatment is recorded as "Drug withdrawn".

TEAE Leading to Death

A TEAE leading to death is defined as a TEAE where the outcome is recorded as "Fatal". Date of death is recorded on the 'Study Termination' eCRF page.

Severe AE

An AE is classed as severe if the Severity is recorded as "Severe", or if the severity is missing.

Relationship to Study Treatment

A TEAE is classified as 'Related' to Study Treatment if the relationship to study drug was recorded (on the 'Adverse Events' eCRF page,) as "Unlikely", "Possible", "Probable" or "Definite". An AE is classified as unrelated to study medication if the relationship to study medication was recorded as "Not Related". Adverse events with unknown relationship to Study Treatment are counted as 'Related' to Study Treatment.

Urine Pregnancy

Urine pregnancy data are recorded at screening and Day 21 on the "Urine Pregnancy Test" eCRF page for female subjects. The following variables are collected:

- Childbearing potential ("Yes", "No")
- Test performed ("Yes", "No")
    - Reason if not performed
- Date of Test
- Result ("Negative", "Positive")

8. Analysis Methods

8.1 General Methods

Post-Text TLFs are provided in collated electronic PDF files.

For continuous variables, the mean, standard deviation, minimum, median and maximum are presented, together with the total number of observations and the number of missing and non-missing values. Unless otherwise specified, minimum and maximum values are reported to the same number of decimal places as the recorded measurements; mean and median are reported to one more decimal place and standard deviation one additional decimal place more than the mean.

For categorical variables, absolute and relative frequencies are reported. Relative frequencies are based on all observations and reported as percentages to one decimal place. Unless otherwise specified, percentages are based on the number of subjects with data and are not calculated for missing categories.

Adverse events are reported on a per-subject basis, i.e. if a subject reported several events coded to the same coding term the subject is counted only once at the respective level of display. The percentages are calculated using the number of subjects in the population Analysis Set as the denominator.

All hypotheses are tested at a 5% level of significance using a two-sided test unless otherwise specified.

P-values are rounded to three decimal places. If a p-value is less than 0.001 it is reported as "<0.001." If a p-value is greater than 0.999 it is reported as ">0.999.

8.2 Specific Methods for Efficacy Analyses

For the primary and secondary endpoints where the data is collected through the activity tracker, only subjects who meet the minimum wear threshold will be included in the analysis. This is defined as a minimum of 3 valid days during the baseline period and a minimum of 3 valid days within each post-baseline 7-day period, where a valid day is defined as a minimum wear of 20 hours per day.

8.2.1 Hypothesis and Testing Strategy

The primary and secondary efficacy endpoint analyses aim to demonstrate that there is a difference between baseline and post-baseline in the variable of interest for each endpoint. More formally, the following hypothesis will be tested:

H_0: There is no difference between baseline and post-baseline (Days 7, 14 and 21) in the endpoint of interest.

H_1: There is a difference between baseline and post-baseline (Days 7, 14 and 21) in the endpoint of interest.

8.2.2 Primary Analysis

The primary efficacy endpoint is the average MVPA at Days 7, 14 and 21 as detailed in section 7.4.7.1.

The primary analysis will follow a hierarchical approach as follows:

1. A Mixed Model with Repeated Measures (MMRM) is used to analyse the change from baseline in MVPA average minutes as the response variable with baseline as a fixed effect. Subjects will be included as a random effect, and timepoint will be treated as a

repeated measure within each subject (with compound symmetry structure between visits). If the parameter for the intercept is found to be statistically significant (p-value < 0.05), then the second model below will be used.

2. A Mixed Model with Repeated Measures (MMRM) is used to analyse the change from baseline in MVPA average minutes as the response variable with baseline and timepoint (with unstructured covariance structure between visits) as fixed effects. Adjusted means for each timepoint will be presented along with p-values and 95% confidence intervals (CIs) for the mean change from baseline in MVPA.

Other than the global test for an overall change from baseline (i.e., intercept), there will be no other adjustment for multiplicity. If data are found to be non-normal, the Friedman Test will be used. If the Friedman test is found to be significant then Wilcoxon Signed Rank Pairwise Tests are used for each week comparison.

8.2.3 Secondary Analysis

The following secondary endpoints are analysed in the manner as described for the primary endpoint described in section 8.2.2:

- Change from baseline on Days 7, 14, and 21 in Daily Average number of steps taken.
- Change from baseline on Days 7, 14, and 21 in Ratio of sedentary/non-sedentary time.
- Change from baseline on Days 7, 14, and 21 in Gait, assessed through speed and step irregularity (measured via cadence and gait speed).
- Change from baseline on Days 7, 14, and 21 in Indices of morning stiffness (assessed through levels of mobility 30- and 60-mins post-wake).
- Change from baseline in self-reported pain intensity, assessed through Numeric Rating Scale (NRS) on Days 7, 14 and 21.
- Change from baseline in WOMAC Physical Function subscale on Days 7, 14, and 21.
- Change from baseline in the WOMAC subscales, Pain (composite) and Stiffness (composite) on Days 7, 14, and 21.
- Change from baseline in the WOMAC Global Score on Days 7, 14, and 21.

The secondary endpoint, study subjects' perceived ability to exercise more regularly, assessed using the WOMAC Physical Function subscale on Days 7, 14, and 21, will be analysed by exploring the correlation between WOMAC Physical Function subscale on Days 7, 14, and 21 and the average MVPA as detailed in section 7.4.7.1 (primary endpoint variable) graphically, by means of Spearman rank correlation.

The following secondary endpoints are analysed by descriptive statistics with no formal statistical hypothesis testing performed:

- MVPA on each day of the study (Baseline to final treatment day 21).
- Change from baseline in Karolinska Sleepiness Scale on Days 7, 14, and 21.
- Change from baseline in Health-related quality of life, EQ-5D-5L, on Days 7, 14, and 21.

8.2.4 Exploratory Analysis

Correlations between Voltaren usage, pain relief and mobility and quality of life indices throughout the trial.

Correlations between Voltaren usage, pain relief and mobility and quality of life indices will be explored graphically by means of a heatmap showing the extent of computed Spearman rank correlation coefficients among all QoL indices.

Elapsed time from Voltaren Gel use to achieving time to meaningful pain relief to end of study

Time to meaningful pain relief is estimated using Kaplan-Meier method. This includes, patients with event, patients censored, time to meaningful pain relief (days), median with 95% confidence interval, Q1 and Q3. Time to event and censoring are derived as explained in section 7.4.7.3.

8.2.5 Statistical/Analytical Issues

8.2.5.1 Handling of Dropouts or Missing Data

In the derivation of endpoints there is no replacement of missing data except for adverse event dates as detailed in section 7.2.2.

The primary and secondary analysis method employs mixed-model with repeated measures analysis techniques which use information from the observed data, likelihood-based estimation, subject-specific effects and the within-subject correlation structure to provide information about the unobserved data (although missing data are not explicitly imputed). This analysis uses the available data to provide information about the unobserved data and estimates the treatment effects assuming the withdrawn subjects has the same statistical behaviour as those who continue. Data is not imputed for this type of analysis.

Missing data due to general dropout/withdrawals will be assessed on an ongoing basis during the study. Any further sensitivity analyses needed due to missing data will be reviewed at the time of data review.

8.2.5.2 Data Review

The process starts with the Statistician writing a Data Review Meeting (DRM) plan and based upon this approved plan, then a DRM will occur prior to database lock. The process ends with the approval of a formal meeting report which describes the decisions made at the data review meeting.

The SAP will be reviewed after the DRM and may be updated if deemed applicable. Details for the DRM will be provided in DRM plan that will cross-reference to the SAP.

8.2.5.3 Multiple Comparisons/Multiplicity

No account for multiple comparisons or multiple testing is performed, as a hierarchical strategy is applied for the primary efficacy endpoint as detailed in section 8.2.2.

9. Interim analyses

No interim analysis is planned for this study.

10. Overview of Tables, Listings and Figures

Below is a list is given per topic with variables and populations used in tables. For the content, titles and layout of the full set of tables see the table shells in the appendix.

10.1 Disposition of Subjects

Table CCI summarizes the disposition of subjects in the Total Set by treatment and overall. This includes a summary of the number (n) and percentage (%) of: subjects screened; subjects who are screen failures; subjects who are enrolled; subjects who completed the study; subjects

who discontinued the study and the primary reason for discontinuation. Percentages are based on the number of subjects enrolled, percentages are not shown for the number of subjects screened or the number of screening failures.

The number of subjects who attended scheduled visits in clinic and eDiary is summarized in Table CCI (Visit Attendance) by absolute counts (n) and percentages (%), by treatment and overall, for the Enrolled Population.

Listing CCI presents reason for screening failures for all screen failure subjects in the Total Set.

Listing CCI presents disposition data, including informed consent dates, completion status and the primary reason for study discontinuation, for the Total Set.

10.2 Protocol Deviations

Listing CCI presents all major protocol deviations for the Enrolled Population.

10.2.1 Inclusion and Exclusion Criteria

The eligibility of all subjects for entry into the study is assessed at the screening visit by the Inclusion and Exclusion criteria ('Subject Eligibility: Inclusion/Exclusion Criteria eCRF page).

Listing CCI presents all subjects who failed to meet all of the inclusion and Listing CCI CCI presents all subjects who met any exclusion criteria, along with all their inclusion and exclusion responses, for the Total Set.

10.3 Data Sets Analysed

The number of subjects in each Analysis Set defined in Section 6.1 is summarized by absolute counts (n) and percentages (%), by treatment and overall, for the Enrolled Population in Table CCI

Listing CCI presents the inclusion into each Subject Analysis Set defined in 'Section 6.1', including the primary reason for exclusion from the SAF and mITT, for the Enrolled Population.

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics

Descriptive statistics [number of subjects (n), mean, SD, median, minimum and maximum and percentage (%) of subjects] will be presented for demographic characteristics, by treatment and overall. These variables include age (years), sex, race, and ethnicity and will be presented for the Enrolled Population in Table CCI. Percentages are based on the number of subjects with data.

Table CCI summarizes demographic characteristics for the Enrolled Population for US only subjects.

Table CCI summarizes demographic characteristics for the Enrolled Population for EU (Poland) only subjects.

Listing CCI presents all demographic data for the Enrolled Population.

10.4.2 Medical History

Listing CCI presents all medical history data for the Enrolled Population.

Listing CCI presents knee osteoarthritis diagnosis data for the Enrolled Population.

10.4.3 Prior and Concomitant Medications

Listing CCI presents all prior and concomitant medication data for the Enrolled Population.

Listing CCI presents all concomitant procedure data for the Enrolled Population.

10.4.4 Visual Analogue Scale

Listing CCI presents all VAS data for the Total Set.

10.5 Study Medication

10.5.1 Measurements of Treatment Exposure and Compliance

Treatment exposure and compliance data, including collected and derived, are summarized by summary statistics, by treatment and overall, for the SAF in Table CCI

Listing CCI presents all treatment exposure and compliance data for the SAF.

Listing CCI presents all device accountability data for the SAF.

Listing CCI presents all medical product accountability data for the SAF.

Listing CCI presents all study product use data for the SAF.

10.6 Efficacy Results

10.6.1 Primary Efficacy Analysis

Table CCI summarizes change from baseline in the average minutes of MVPA at day 7, day 14 and day 21 by summary statistics by timepoint along with the analysis results specified in section 8.2.2 for the mITT.

Figure CCI presents MVPA over time for the mITT.

Listing CCI presents all MVPA data for the mITT.

10.6.2 Secondary Efficacy Analysis

Change from baseline at day 7, day 14 and day 21 tables are summarized by summary statistics by timepoint along with the analysis results specified in section 8.2.3 for the mITT, for each of the following secondary endpoints:

- Daily Average number of steps taken in Table CCI
- Ratio of sedentary/non-sedentary time in Table CCI
- Gait, assessed through speed and step irregularity in Table CCI
- Indices of morning stiffness in Table CCI
- WOMAC scores including Pain, Stiffness and Physical function subscales in Table CCI
- NRS in in Table CCI

Change from baseline at day 7, day 14 and day 21 tables are summarized by summary statistics by timepoint for the mITT, for each of the following secondary endpoints:

- MVPA on each day of the study in Table CCI
- Karolinska Sleepiness Scale in Table CCI
- EQ-5D-5L Index in Table CCI

Table CCI summarizes EQ-5D-5L response data over time by treatment and overall.

Listings CCI present all data for each of the endpoints for the mITT.

Figures CCI presents over time graphs for each of the endpoints for the mITT.

Figure CCI presents the correlation between WOMAC scores and MVPA for the mITT.

10.6.3 Exploratory Analysis

A Kaplan-Meier analysis is performed on the time to meaningful pain relief data on the mITT population as described in section 8.2.4. Table CCI summarizes the number of patients with event, the number patients with censoring, the median time to meaningful pain relief with its 95% CI as well as Q1 and Q3.

Listing CCI presents the time to meaningful pain relief data for the mITT.

Figure CCI presents the Kaplan-Meier graph for the mITT.

10.7 Safety Results

10.7.1 Adverse Events

10.7.1.1 Brief Summary of Adverse Events

An Overview of AEs including but not limited to

- the number of subjects with at least one AE;
- the number of subjects with at least one pre-treatment AE;
- the number of subjects with at least one TEAE;
- the number of subjects with at least one Serious TEAE;
- the number of subjects who permanently discontinued Study Treatment due to a TEAE;
- the number of subjects with a TEAE related to study treatment;
- the number of subjects who had a TEAE with outcome of death
- the worst severity of any TEAE experienced by each subject with at least one TEAE

is summarized by treatment and overall, for the SAF in Table CCI

10.7.1.2 Display of Adverse Events

Adverse event descriptive tables are summarized on a per-subject basis (i.e. if a subject reported the same event repeatedly the subject is counted only once at the specific level of display) and on a per event basis. Absolute counts (n) and percentages (%) are presented for the number of subjects with at least one adverse event, and per SOC and per PT within SOC, by treatment and overall, for the SAF. Percentages are based on the number of subjects in the population. Descriptive tables are sorted alphabetically by SOC and by PT within SOC.

Descriptive tables are ordered by descending frequency of the overall number of subjects within each SOC, and then ordered within each SOC by the overall number of subjects within each PT. In the event of equal frequencies tables are ordered alphabetically.

TEAEs are summarized for the SAF, as follows:

- TEAEs in Table CCI
- Serious TEAEs in Table CCI
- Related TEAEs in Table CCI

10.7.1.3 Listing of Adverse Events

Listing CCI presents all Adverse Event data (raw, derived, and coded), for the SAF.

10.7.2 Other Safety

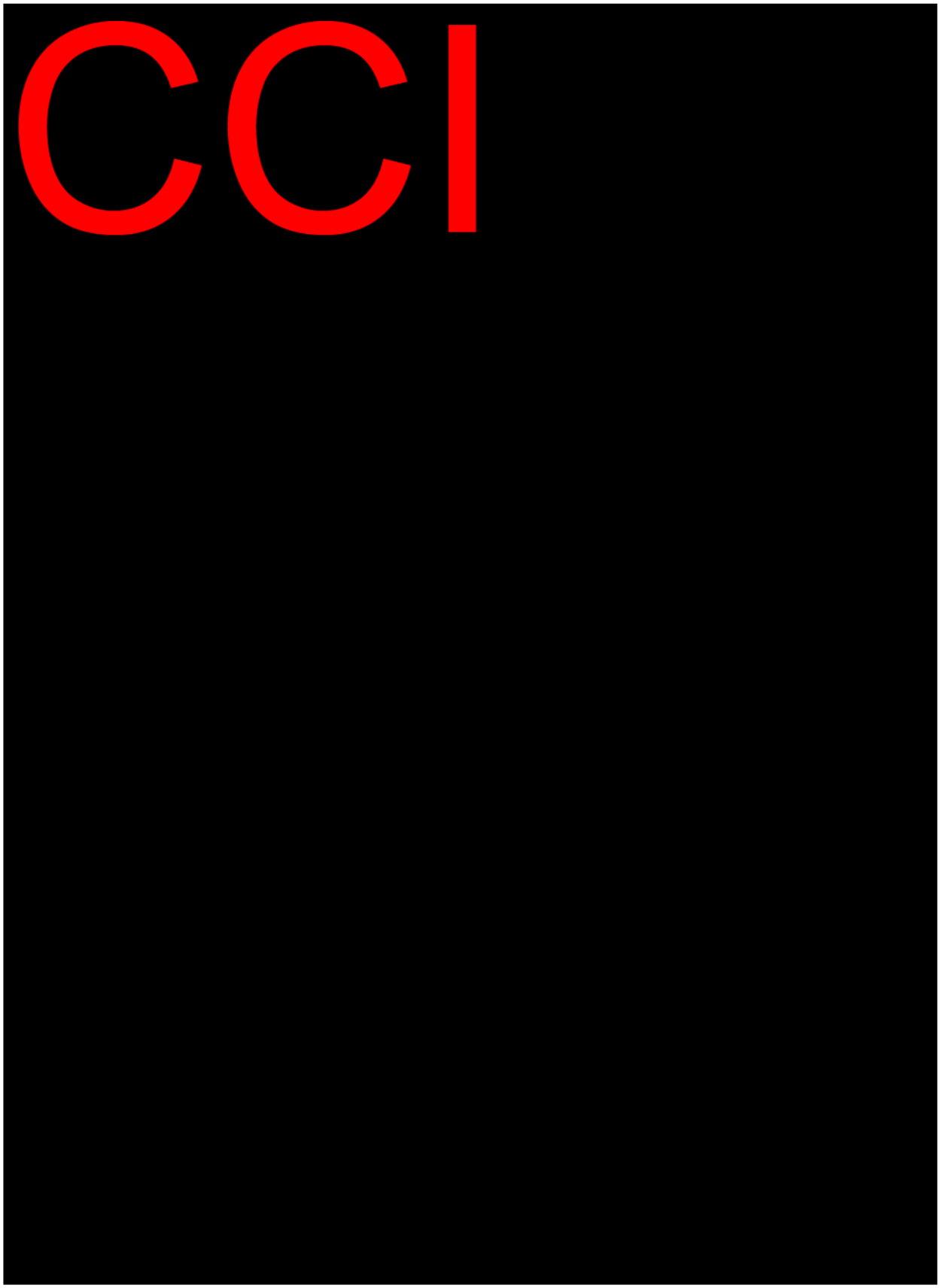
Listing CCI presents all end of study questionnaire data for the SAF.

Listing CCI presents all urine pregnancy data for the SAF.

11. References

[1] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833–40.

12. Tables, Listings and Figures



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13. Appendices

Exact specifications of the data to be provided detailed in a separate mock shell document.

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