CLINICAL PROTOCOL

Protocol Number	300128
Study title	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.
Indication studied	Knee Osteoarthritis (Pain)
Development phase of study	IV
Compound / product name	Voltaren Gel 1% (Diclofenac sodium 1%) Voltaren Gel 1.16% (Diclofenac diethylammonium 1.16%) Voltaren Gel 2.32% (Diclofenac diethylammonium 2.32%)
United States (US) Investigational New Drug (IND) Number:	Not Applicable
Clinical Trial Information System (CTIS) Number:	2024-510839-22-00
Other Regulatory Agency Identified Number:	Not Applicable
Description	This prospective real-world evidence study, conducted in a hybrid format, focuses on assessing the impact of Voltaren Gel on functional mobility and quality of life (QoL) in individuals with mild/non-serious osteoarthritis (OA) of the knee. The study spans multiple countries, including the United States and the European Union.
Sponsor Name & Legal Registered Address	Haleon (CH SARL) Route de l'Etraz 2 Case Postale 1279 1260 Nyon 1 Switzerland
Name of company/sponsor signatory	PPD
Sponsor Contact Details	Haleon (UK) St. George's Avenue Weybridge KT130DE United Kingdom (UK)

CRO Name	CCI [redacted]
CRO Contact Details	CCI [redacted]

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	• Schedule of activities updated to include Urine Pregnancy Test • Exclusion criteria 13 updated to align with Section 11.7.1 • Section 11.7.1 updated to include wordings from CTFG 21/09/2020 V1.1 • Section 14.6 updated to include wording surrounding art. 58 Regulation 536/2014 - archive the content of the clinical trial master file • Section 14.5 updated to include publication policy of the trial data being uploaded to the CTIS database within one year after end of trial in accordance with CTR Annex IV. • Section 14.3.2 updated to includes statement that the clinical trial will be conducted in compliance with Regulation [EU] No 536/2014. • Section 5.3 updated to include clear definition of the end of the trial. • New section 11.8 Reporting Serious Adverse Events and Other Safety Issues to Regulatory Authorities/ Ethics Committees added • New section 11.9 Risks and benefits related to the participation in the clinical trial including a risks/benefits evaluation.
Amendment 2	3.0	• Secondary Endpoint: Daily Average number of stairs climbed/descended endpoint removed as they cannot be measured by Actigraph in a clinically validated manner. • Semantic clarifications on secondary endpoints. • Schedule of activities (Table 1-1) updated to provide clarity on dispensing of Actigraph device and usage of QoL questionnaires. • Inclusion criteria 6 further clarified to include evidence which can be accepted to confirm OA. • Exclusion criteria 10 further clarified to provide clear definition of exclusion of patients. • Section 7.8 updated to align with inclusion/exclusion criteria and to avoid confusion within text. • Section 11.3.2 updated to include Table 11-1 with updated Single Case Processing Group mailbox. • Semantic update in Section 13.2 to provide more clarity on population analysis. • Semantic update in Section 13.3.2 to provide more clarity for secondary analysis. • Section 16.3.1 (End of Study questions) updated to include redrafted stairs ascending/descending question as end of study question.
Amendment 3	4.0	• Section 5.3 updated to include clear definition of the end of the study.

New versions incorporate all revisions to date prior to submission to country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	PPD
Investigator Qualifications:	PPD
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD dd-mmm-yyyy

Table of Contents

List of in text tables

1 PROTOCOL SUMMARY

Title of Study	A Prospective Real-World Evidence Study evaluating the effects of Voltaren use on Mobility and QoL of subjects with knee osteoarthritis (OA) pain.
Protocol Number	300128
Investigators/Study Sites	Study Sides: 8 Countries: United States and European Union (Poland)
Phase of Development	Phase IV (Real World Evidence Study)

Objectives	The purpose of the study is to investigate how topical diclofenac use can improve functional mobility and physical activity primarily, as well as other quality-of-life parameters such as sleep, mood, and engagement in daily activities. Primary Objective: • To evaluate the effects of Voltaren Gel on physical activity, measured through connected activity tracker. Secondary Objectives: • To evaluate the effects of Voltaren Gel on functional mobility, measured through connected activity tracker. • To assess the functional mobility, measured through 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. Exploratory: • To explore the link between Voltaren usage, level of pain relief and functional mobility/quality of life • To evaluate time-to meaningful pain relief after Voltaren Gel use. Safety: • To monitor adverse events (AEs) during study period.

Study Endpoints	**Primary endpoint:** Change from baseline in the average minutes of Moderate and Vigorous Physical Activity (MVPA), at Week 1 (days 1-7), Week 2 (days 8-14), and Week 3 (days 15-21). **Secondary endpoints:** Change from baseline on Days 7, 14, and 21 in: • Daily Average number of steps taken • Ratio of sedentary/non-sedentary time • Gait, assessed through speed and step irregularity (measured via cadence and gait speed) • Indices of morning stiffness (assessed through levels of activity 30- and 60-mins post-wake) Indices of level of stiffness throughout the day as assessed via the WOMAC stiffness subscale Change from baseline in: • WOMAC Physical Function subscale on Days 7, 14, and 21 • Study subjects' perceived ability to exercise more regularly. Assessed using the WOMAC Physical Function subscale on Days 7, 14, and 21 • Change from baseline in self-reported pain intensity, assessed through Numeric Rating Scale (NRS) (daily assessment) Change from baseline in the WOMAC total score and subscales on Days 7, 14, and 21: • Pain (composite) • Stiffness (composite) Change from baseline in on Days 7, 14, and 21 • Sleep/alertness: Karolinska Sleepiness Scale assessed 1x/day. • Health-related quality of life: EQ-5D-5L **Exploratory endpoints:** • Correlations between Voltaren usage, pain relief and mobility and quality of life indices throughout the trial. • Elapsed time from Voltaren Gel use to achieving time to meaningful pain relief to end of study.
Estimands	N/A

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, together with the use of subjective assessments, to provide first-ever 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. Approximately 195 subjects are expected to be enrolled in the study, with an anticipation that approximately 147 of these subjects will successfully complete the entire study. 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. Study period for each subject will last a maximum of 28 days.

Selection of Subjects	Main Inclusion Criteria: • A Subject between the age of 40 and 85 years. • A subject with diagnosed knee mild/non-serious osteoarthritis, proven via radiological evidence collected within the last 3 years. • A subject with self-reported knee pain, with a score of ≥ 40 mm ≤ 70mm on the pain intensity visual analogue scale at the Screening Visit. • A subject willing to use Voltaren Gel for up to 3 weeks. Main Exclusion Criteria: • A subject with confirmed rheumatologic disease. • A subject who has experienced trauma to the knee within the last 2 months that resulted in pain and/or swelling. • A subject that has been administered local steroids or other NSAIDs injections to the knee within the last 6 months. • A subject with recent history of major knee injury or surgery. • A subject with knee skin area pathological condition which prevents application of product to the skins. Conditions such as: open skin wounds, infections, inflammations, or exfoliative dermatitis conditions. • A subject who is pregnant, lactating or plan to be pregnant or lactating during the study.

Planned 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.
Investigational Therapy	Voltaren Gel 1% (diclofenac sodium) (US Only) Voltaren Gel 1.16% (diclofenac diethylammonium) (EU Only) Voltaren Gel 2.32% (diclofenac diethylammonium) (EU Only)

Treatment Duration/Intervention	Actigraph device will be provided post patient consent at Day -7 to collect baseline information. The baseline period will last between 3 (minimum) and 7 days (maximum), to collect enough information on both subjective and objective aspects of mobility and sleep quality. End of baseline period will be considered day 0. Post baseline period, (at Day 7 of the study) subjects will be provided with the product (Voltaren) and Actigraph device where there will be a total of 21 days of product usage and assessment of parameters as highlighted in the objectives. Each subject will be in the study for 28 days maximum.
Safety	Number and percent of study subjects reporting AEs or serious AEs (SAEs) while on treatment. • Treatment Related. • Non-Treatment Related.

Statistical Methods and Planned Analyses	For the primary objective, a Mixed Model with Repeated Measures (MMRM) will be used to analyse the change from baseline in MVPA average minutes as the response variable. Subject will be included as a random effect. Average minutes of MVPA over Week 1 will be calculated over all non-missing days between study day 1 (product usage) through 7, inclusive. Average minutes of MVPA over Week 2 will be calculated over all non-missing days between study day 8 through 14, inclusive. Average minutes of MVPA over Week 3 will be calculated over all non-missing days between study day 15 through 21, inclusive. Any days beyond day 23 will be excluded from all summaries and analyses and will only be present in listed data. For the secondary objective, functional mobility as measured through wearables and PRO, pain intensity assessed through NRS (daily assessment), activity-related pain and stiffness as measured in the (Likert Scale) WOMAC subscales for composite pain and composite stiffness will be analysed in the same manner as the primary objective. For the exploratory endpoints, correlations between pain relief, mobility, and quality of life indices will be measured throughout the trial. Additionally, the use of concomitant medications and any changes in use of pain relief medications will be recorded throughout the trial. Time to pain relief will be evaluated using Kaplan-Meier curves of QoL factors. The median time to resolution of symptoms based on the Kaplan-Meier curve will be presented as well.

1.1 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being.

This study adopts a hybrid approach, wherein participants are only obligated to be physically present for on-site screening (Day -7 – Visit 1), end of baseline (Day 0– Visit 2), and end-of-study visits (Day 21– Visit 3). The remaining treatment phase (Day 1-21) will be conducted at home or in areas of interest to observe the real-world evidence (RWE) usage of the product. Study period will last a maximum of 28 days.

Table 1-1 Schedule of Activities

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
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

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)
Study Conclusion									
Returning Actigraph device and the allocated product									X
End of Study Questionnaires									X

Footnotes:

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.

2 INTRODUCTION

Real world evidence (RWE) studies provide an opportunity to gather information on the real-life effectiveness of a product in a population that is reflective of the consumer base. The present study aims to use a prospective RWE design to assess the real-life impact of using Voltaren Gel (diclofenac) on functional mobility and quality of life. This is the first Haleon study that will go beyond subjective assessment of these benefits, using research-grade wearable devices (Actigraph) to accurately measure changes in functional mobility and aspects of quality of life (O'Brien et al. 2020). Together with objective and subjective assessments of these benefits, this study will provide us with first-ever subject-centric data on the real-world benefits of using Voltaren, beyond pain relief.

2.1 Study Rationale

This study is designed to assess the real-life impact of using Voltaren Gel (diclofenac) on functional mobility and quality of life. This study will utilise a research-grade validated wearable device: Actigraph, to accurately measure objective changes in functional mobility.

2.2 Background

Topical diclofenac products are well-established globally for the treatment of pain and inflammation due to acute trauma (sprains, strains, muscle aches, sports injuries) as well as for the relief of mild/non-serious osteoarthritis pain. Topical Non-steroidal anti-inflammatory drugs (NSAIDs) which are applied locally to the site of symptoms penetrate the skin and permeate to deeper tissues to exert a therapeutic effect (Hagen and Baker, 2017). Clinical studies of topical NSAIDS in OA of the hand and knee have demonstrated statistically significant and clinically meaningful pain relief (Barthel et al 2009, Altman et al 2011).

With regards to osteoarthritis, the primary goal of disease management is to control symptoms, such as pain and impaired function (Jordan et al 2003, Kloppenburg et al 2019). A network meta-analysis found that NSAIDs are the most effective individual treatment to improve pain and function in osteoarthritis (Jevsevar et al 2018). The authors conclude that topical diclofenac, regardless of dose, had the largest effect on pain and physical function compared to other topical treatments including NSAIDs. In a recent meta-analysis of 192 clinical trials, the authors assessed the effectiveness and safety of different preparations and doses of NSAIDs, opioids, and paracetamol to help health care providers manage knee and hip OA pain and physical function (Da Costa et al. 2021).

The use of topical NSAIDs is recommended in evidence-based treatment guidelines focused on the management of OA. Topical NSAIDs are recommended by the American College of Rheumatology (ACR) and the Osteoarthritis Research Society International (OARSI) for the symptomatic treatment of OA of the knee. Additionally, the ACR also strongly recommends topical NSAIDs for patients/subjects with knee OA, and notes that topical NSAIDs should be considered prior to the use of oral NSAIDs, to minimize systemic exposure (Kolasinski et al 2019). The OARSI guidelines strongly recommend topical NSAIDs for knee OA patients/subjects with and without gastrointestinal or cardiovascular comorbidities and for patients/subjects with frailty (Bannuru et al 2019).

Despite these well-established beneficial effects of diclofenac for the treatment of pain and inflammation in OA, the real-life mobility and quality of life benefits of using diclofenac for pain relief have not been examined. Considering the large impact that knee OA pain could have on subjects ability to move, exercise, and perform daily activities, it is highly likely that

diclofenac related pain relief can lead to substantial improvement in people's quality of life (Van Walsem et al 2015). According to the ACR, exercise is considered a highly effective and recommended intervention in knee OA, thereby conceptualizing mobility not only as an outcome that is affected by knee OA but also as an enabler of improved disease outcomes in OA (Kolasinski et al 2019). The purpose of the study is to investigate how topical diclofenac use can improve functional mobility and physical activity primarily, as well as other quality-of-life parameters such as sleep, mood, and engagement in daily activities.

2.3 Mechanism of Action/Indication

Voltaren Gel contains diclofenac as an active ingredient. It is a nonsteroidal anti-inflammatory drug (NSAID) that is used for the treatment of inflammation and pain. The primary mechanism responsible for these effects is thought to be the inhibition of prostaglandin synthesis via inhibition of Cyclooxygenase 1 (COX-1) and COX-2.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the effects of Voltaren Gel on physical activity, measured through connected activity tracker.	Change from baseline in the average minutes of Moderate and Vigorous Physical Activity (MVPA), at Week 1 (days 1-7), Week 2 (days 8-14), and Week 3 (days 15-21).
Secondary	
To evaluate the effects of Voltaren Gel on functional mobility, measured through connected activity tracker	Change from baseline on Days 7, 14, and 21 in: • Daily Average number of steps taken • Ratio of sedentary/non-sedentary time • Gait, assessed through speed and step irregularity (measured via cadence and gait speed) • Indices of morning stiffness (assessed through levels of activity 30- and 60-mins post-wake) Indices of level of stiffness throughout the day as assessed via the WOMAC stiffness subscale Change from baseline in: • WOMAC Physical Function subscale on Days 7, 14, and 21
To assess the functional mobility, measured through connected activity tracker.	Moderate and Vigorous Physical Activity (MVPA) on each day of the study (Baseline to final treatment day 21).
To evaluate the effects of Voltaren Gel on functional mobility, measured through subject related outcomes	Study subjects' perceived ability to exercise more regularly. Assessed using the WOMAC Physical Function subscale on Days 7, 14, and 21
To evaluate the effects of Voltaren Gel on pain intensity	Change from baseline in self-reported pain intensity, assessed through Numeric Rating Scale (NRS) (daily assessment).
To evaluate the effects of Voltaren Gel on activity-related pain and stiffness	Change from baseline in the WOMAC total score and subscales on Days 7, 14, and 21: • Pain (composite) • Stiffness (composite)

To evaluate the effects of Voltaren Gel on correlates of quality of life	Change from baseline in on Days 7, 14, and 21 • Sleep/alertness: Karolinska Sleepiness Scale assessed 1x/day. • Health-related quality of life: EQ-5D-5L
Safety	
To monitor any record adverse events (AEs) during study period.	Number and percent of study subjects reporting AEs or serious AEs (SAEs) while on treatment. • Treatment Related. • Non-Treatment Related.
Exploratory	
To explore the link between Voltaren usage, level of pain relief and functional mobility/quality of life	Correlations between Voltaren usage, pain relief and mobility and quality of life indices throughout the trial.
To evaluate time-to meaningful pain relief after Voltaren Gel use	Elapsed time from Voltaren Gel use to achieving time to meaningful pain relief to end of study.

4 ESTIMANDS

Not Applicable.

5 STUDY DESIGN

This prospective open-label, single-arm, multi-country (US and EU) real-world evidence study (RWE) study, conducted in a hybrid format focusing on assessing the impact of Voltaren Gel on functional mobility and quality of life (QoL) in individuals with mild/non-serious osteoarthritis (OA) of the knee.

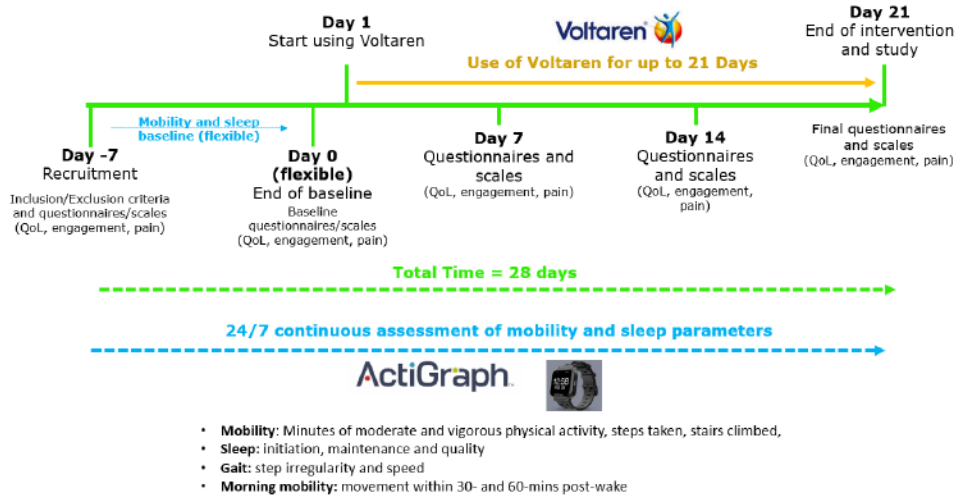
The target population comprises adults aged between 40 and 85 years, diagnosed with knee mild/non-serious osteoarthritis and self-reporting pain at the time of recruitment. Approximately 195 subjects are expected to be enrolled in the study, with an anticipation that around 147 of these subjects will successfully complete the entire study.

In this hybrid study design, participants will be required to physically attend on-site visits for screening, baseline assessments, and end-of-study evaluations. However, for the remainder of the study period, data collection will be executed remotely following the guidelines provided by CCI utilising an (electronic) eDiary system.

In the EU, two variants of Voltaren Gel are available, namely 1.16% and 2.32% DDEA. During the screening and enrolment process, the investigator will assess the subjects' product preference as well as the need and the severity of osteoarthritis (OA) to determine and dispense the appropriate percentage of gel. The aim is to include a minimum of 25 patients utilising the 1.16% Voltaren Gel to enable understanding of real-world usage for the 1.16% Voltaren variant.

Advertisements approved by (Investigation Review Board) IRBs/ Ethics Committee (ECs) and investigator databases may be used as recruitment procedures. Use of EC approved generic, pre-screening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed.

Haleon will review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.



5.1.1 Limitations of the study

Given the natural course of OA and pain, data collected during this study may be confounded by the natural course of the disease. Within 24 hours of pain onset, subjects generally report an increase in the severity and number of symptoms they experience.

Given the natural course of the disease, ensuring subjects have access to treatment when OA symptoms are present will allow for subsequent quality of life (QoL) data to be captured, reducing the influence of confounding variables.

Subjects may likely be using other over-the-counter antipyretics/analgesics for severe pain, which may influence their overall Actigraph and QoL data and confound the effect of Voltaren. During this study, subjects will be prompted to report medications they take for symptom relief, along with any changes in medication over the course of their study participation, to better understand the results.

Actigraph is as a clinically approved, research-grade, and validated device. It boasts commendable accuracy and applicability in its device and algorithm, ensuring reliable data quality. While some limitations of its usage in a real-world environment may exist, the device's robust design minimises the likelihood of false data, affirming its overall dependability. However, subjects may not be comfortable wearing a wearable device continuously as well as subject non-wear compliance and user related errors may have an impact on the data collected.

At the start of the study, site staff will be given training by Actigraph or relevant trained personnel or through online videos on how to use the device (see tutorial link in appendix), with training on how to use and wear the device appropriately. After receiving training, site staff can then appropriately train subjects, particularly during the dispensing of the product.

5.2 Justification for Dose

The study plans to collect and evaluate data from all Voltaren topical marketed doses. Dosing instructions will be followed as listed on the study product commercial label.

5.3 End of Study and Clinical Trial Definition

A subject is considered to have completed the study if they have completed all procedures and assessments of the study including the last scheduled procedure shown in the Schedule of Activities.

Subjects will have the option to discontinue treatment at their discretion, if they determine they no longer want treatment. The reasons for discontinuing treatment will be captured whenever possible. The end of this study is defined as last visit of the last subject. At the end of the study each study subject shall complete an exit survey as detailed in the appendix.

6 STUDY POPULATION

6.1 Type and Planned Number of Subjects

Adults between 40-85 years of age with a diagnosis of knee osteoarthritis and self-reported pain at recruitment will undergo screening for inclusion in the study. Anticipating a dropout rate of approximately 25%, the trial aims to enrol a total of 195 eligible subjects, with an expected completion rate of approximately 147 study participants.

Eligibility criteria for participation in the study include adult subjects diagnosed with knee osteoarthritis, supported by radiological evidence obtained within the last three years. Additionally, participants must self-report knee pain, registering a score of ≥ 40 mm and ≤ 70 mm on the pain intensity visual analogue scale (VAS). Prospective participants must express willingness and ability to adhere to scheduled visits, follow an on-label Voltaren gel use, comply with other study procedures, and commit to using Voltaren gel for up to three weeks. For comprehensive details, refer to the inclusion and exclusion criteria provided below.

A Screened subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorised representative.

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly or via their legally authorised representative and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

This study can fulfil its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

Subject eligibility to participate in the clinical study should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

6.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible to be included into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 40 and 85 years, inclusive.

3. A subject who is willing and able to comply with scheduled visits, on-label Voltaren Gel use plan, and other study procedures.
4. A subject willing to wear Actigraph continuously 24/7 for the study period.
5. A subject in good general and mental health.
6. A subject with diagnosed knee mild/non-serious osteoarthritis, proven via radiological evidence collected within the last 3 years (Any documentation that indicates mild/moderate OA is acceptable – such as Kellgren/Lawrence (K/L) method of assessment).
7. A subject with self-reported knee pain, with a score of ≥ 40 mm ≤ 70mm on the pain intensity visual analogue scale at the time of Informed Consent Form (ICF) signature.
8. A subject willing to use Voltaren Gel for up to 3 weeks.
9. A subject of potential childbearing willing to follow an effective method of contraception (as listed below in section 11.7) from the time of screening (post consent prior to the use of product) and up to end of study visit.

6.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or a Haleon employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 1 month prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject with confirmed rheumatologic disease
5. A subject who has experienced trauma to the knee within the last 2 months that resulted in pain and/or swelling.
6. A subject that has been administered local steroids or other NSAIDs injections to the knee within the last 6 months.
7. A subject with recent history of major knee injury or surgery.
8. A subject with knee skin area pathological condition which prevents application of product to the skins. Conditions such as: open skin wounds, infections, inflammations, or exfoliative dermatitis conditions.

9. A subject with conditions not limited to the following: Gastrointestinal diseases, asthma, hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function, or liver disease as judged by investigator or Site Staff.
10. A subject diagnosed with other relevant medical conditions (e.g., psychiatric, neurological - This excludes subjects with well-controlled depression, anxiety or migraines who are on a stable dose of medication which may be allowed – this is up to the discretion of site staff and investigators).
11. A subject who takes medication relating to above conditions, such as tricyclic antidepressants or anticonvulsants
12. A subject with an active infection.
13. A Female subject who is pregnant at Screening as evidenced by a positive UPT, or intending to become pregnant (see section 11.7 Pregnancy).
14. A subject with use of aspirin, Oral Nonsteroidal Anti-inflammatory Drugs, topical treatment with any NSAIDs, warfarin, ACE inhibitors, cyclosporine, diuretics, lithium or methotrexate, corticosteroids, or other anticoagulant therapy within 30 days of study.
15. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients, including hypersensitivity to NSAIDs and aspirin triad.
16. A subject with any other acute or chronic illness that could compromise the integrity of study data or place the subject at risk by participating in the study.
17. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

6.4 Randomisation Criteria

There will be no randomisation of the product as the aim is to obtain real world usage of Voltaren.

6.5 Lifestyle Considerations

Study subjects are expected to continue daily lifestyle activities whilst wearing Actigraph.

Study subjects should wear the Actigraph on the non-dominant wrist to avoid discomfort.

Actigraph is water resistant and can be worn in the shower, bath, or swimming pool. The only restriction is that it cannot be worn when in saltwater (i.e., the ocean). Therefore, where possible study subjects should wear Actigraph continuously 24/7 throughout the day.

Actigraph will be provided fully charged during screening and likely will not need to charge during full duration of the study. Nevertheless, if there are any issues with the

device, the site staff are to be notified immediately, and the device should be replaced to ensure continuation of data collection for that subject for the remainder of the study.

During the study, subject will be asked to press an event button on the Actigraph when they get into bed and when they get up. This will assist in analysing the data and identifying the amount of time spent in bed/awake etc.

Subjects should minimise or avoid Actigraph exposure to natural or artificial sunlight (e.g., sunbeds) whenever possible. Additionally, they should refrain from damaging the product in any way that compromises its integrity, as this is essential for the continuous monitoring of the device throughout the study.

6.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the study but are not subsequently enrolled in the study i.e., do not fulfil all the eligibility criteria.

To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography (year of birth, gender, race), screen failure details (e.g., withdrawal of consent), and eligibility criteria.

Prospective subjects who do not meet the criteria for enrolment in this study (screen failure) may not be re-screened unless due to technical issues within the study or the wearable device. If re-screening is applicable, individuals will be re-invited with a new screening number and reconsented onto the study with new consent form and new subject number.

6.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the Study Contact List (TMF-187870) located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical/ dental questions or problems if the established communication pathways between the investigational site and the study team are not available.

6.8 Rater/Clinical Assessor Qualifications

No rater/clinical assessor qualifications are required for this study.

7 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and Haleon policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

This includes a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

7.1 Investigational/Study Product(s) Supplies

The following study products will be used and will be supplied to the site by the Clinical Supplies Department, Haleon. The site staff will supply one of the products to the study subjects.

Table 7-1 Investigational/Study Product(s) and Device

	Test Product (US only)	Test Product (EU only)	Test Product (EU only)	Actigraph Device
Product Name	Voltaren Gel 1% (diclofenac sodium)	Voltaren Gel 1.16% (diclofenac diethylammonium)	Voltaren Gel 2.32% (diclofenac diethylammonium)	Actigraph wGT3X-BT or similar device provided by Actigraph
Pack Design	Labelled commercial pack	Labelled commercial pack	Labelled commercial pack	Labelled commercial pack
Dispensing Details	As per site discretion	As per site discretion	As per site discretion	One per subject
Product Master Formulation Code (MFC)	US Commercial Product	EU Commercial Product	EU Commercial Product	N/A
Dose/Application	As per label and leaflet instructions	As per label and leaflet instructions	As per label and leaflet instructions	As per label, leaflet or site-specific instructions post training
Route of Administration	Topical	Topical	Topical	N/A (Device worn on wrist)

7.2 Administration

Only subjects enrolled in the study may receive study products and only authorised site staff may supply or administer study products. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the authorized site staff only.

Subjects will be provided product from study teams located in EU (Poland) and US following screening and baseline assessments. Subjects will be asked to follow the marketed product on-label instructions for Voltaren without further instruction from the sponsor or investigator.

For Actigraph, both site staff and subjects will be given training by Actigraph or relevant trained personnel or online videos on how to use the device can also be followed (see tutorial link in appendix).

7.2.1 Medication/Dosing Errors

Medication/dosing errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,

Such medication/dosing errors occurring to a study subject are to be captured in the electronic case report form (eCRF). In the event of medication/dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

Medication/dosing errors are reportable irrespective of the presence of an associated (Adverse Event) AE, including:

- Medication/dosing errors involving subject exposure to any of the study products;
- Potential medication/dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated adverse event(s) are to be captured in the eCRF AE form.

7.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study.

Limited quantities of the study product(s) will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

7.3 Investigational/Study Product(s) Storage and Instructions

The investigator must confirm appropriate temperature conditions have been maintained during transit for all study products received and any discrepancies are reported and resolved before use according to the supplied shipping documentation.

The investigator will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum, and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labelling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation, and reported to the Sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Site staff will instruct subjects on the proper storage requirements for all take-home products. Subjects will be instructed to follow the approved on-label instructions on how to store the product and Actigraph device. For further instructions, subjects can directly follow the details provided during study initiation.

7.4 Investigational/Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for

using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

At the end of the study (Day 28), Actigraph device and the allocated product (used and unused) for this clinical study, should be returned to the Haleon Clinical Supplies Department or CCI using the return instructions provided.

Detailed instructions for the return of study product for the accountability checks and subsequent destruction will be provided by Haleon or CCI during the study in time for study close out visit.

7.5 Blinding and Allocation/Randomisation

Not Applicable.

7.6 Breaking the Blind

Not Applicable.

7.7 Compliance

Study subjects will be told to use the products as per label instructions. Compliance and product use will be monitored throughout the study. Actigraph will collect mobility and sleep-related information continuously (24/7) throughout the study. Subjective questionnaires and items will be administered at pre-specified time-points during the study. Safety, adverse events, and use of concomitant medications will be monitored throughout the study. If a subject stop using the product before Day 28, they will be prompted to complete all relevant questionnaires and items before concluding the study.

Missed assessments will be recorded as such. Exceptions will be made for subjects who report having experienced technical or connectivity issues that prevented them from using Actigraph. If a subject has failed/forgot to press the event button, they should make a note in the eDiary of approximate date/time of missed event.

Compliance will be calculated as an ongoing measure throughout the treatment. For subjects who are withdrawn or withdraw prior to the end of the treatment period, percent adherence will be based on the number of days active in the study intervention prior to withdrawal.

7.8 Concomitant Medication/Treatment(s)

As this is RWE study, concomitant treatments are allowed during the entire period of the study at the discretion of the investigator.

At screening, subjects will confirm their medical history and concomitants medication use to the investigator, and subjects on exclusionary medications will not move forward based on their responses (see exclusion criteria). Thereafter, if any change in concomitant medication is reported while the subject is still enrolled in the study, the investigator will be alerted to fill out the concomitant medications form.

If the concomitant medication needs to be noted, this form will be available for investigator to fill-out. If the subject reports to the investigator incidences of being administered medication, supplements, or vaccines due to a health reason after signing consent, the investigator will note this in concomitant medication form with its indication, unit dose, daily dose, and start and stop dates of administration in the study portal. Please see section 8.1.4 for details on noting medical history and section 12 for AE/SAE monitoring.

The following prohibitions or restrictions for concomitant therapies are in effect during

the study:

- Oral, intramuscular, soft tissues injections of corticosteroids or intra-articular procedure or periarticular injections in the target joint within 6 months prior to enrolment prior to enrolment.
- A subject who takes medication relating to conditions outlined in the exclusion criteria .
- Subjects are strongly advised not to take any disallowed medication; however, subjects were not to be discontinued for intake of disallowed treatment unless there was a safety issue. This is to be judged by the investigator and the site staff. The subjects during the study are permitted to use:
- Nasal sprays with local mode of action, eye drops, and anal ointments are permitted.
- Opiates, NSAIDs or any other analgesics.
- Doses of one or two 500-mg paracetamol/acetaminophen tablets were permitted up to a maximum of 8 tablets (4 g) per day. A minimum of 4 hours between doses are advised and permitted during the study.

The above medication usage will be recorded by investigator at screening and by subjects in eDiary during the study period and must be clearly outlined during the study period where possible.

8 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention

A subject may choose to discontinue or may be discontinued from the study intervention early at any time whilst still in the study at the discretion of the investigator for the following reasons related to safety, subject consent or a potential worsening of the risk / benefit assessment from the subject of remaining on the intervention:

- Adverse Event
- Lack of efficacy from the intervention
- Subject to be withdrawn from the study (see below - section 8.2)

If a subject is discontinued early from the intervention, the reason(s) for discontinuation and the associated date must be documented in the relevant section(s) of the eCRF. The subject should stay in the study and complete the remaining assessments unless they need to be withdrawn (see section 8.2).

8.2 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety.
- Withdrawal of informed consent.
- Subject lost to follow-up.
- Unblinding of the subject.
- Pregnancy.

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the eCRF.

8.3 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the

subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved AEs.

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include the following:

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

Adherence to the study design requirements, including all procedures are essential and required for study conduct.

This section lists the procedures to be completed for each planned study time point. However, as per nature of RWE studies, if a subject fails to complete their daily questionnaires at any timepoint post-baseline, subjects will be permitted to continue in the study with missed dates recorded in the e-dairy.

9.1 Visit 1/ (Pre) Screening

Subjects willing and able to comply with scheduled visits, and use Voltaren Gel as per label, and other study procedures, and are willing to use Voltaren Gel for up to 3 weeks are eligible to take part in the study (for full details see inclusion and exclusion criteria).

Screening procedures will be conducted by the investigator, or suitably qualified designee.

The following data will be collected for screening:

- Informed Consent.
- Urine Pregnancy Test.
- Demographics & Shipping information.
- Screening Questionnaire.
- Medical History/Concomitant medication checklist.
- Pain Visual Analogue Scale to confirm OA levels.
- Numeric Rating Scale for reporting.

Subjects that provide consent will be prompted to continue. investigators will work with subjects and complete the screening questionnaire, confirm their medical history and concomitant medication, and complete their demographics forms. All relevant medical and non-medical conditions should be taken into consideration by the investigator, or suitably qualified designee when deciding whether a particular subject is suitable.

9.1.1 Informed Consent

The investigator must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before any study-specific activity is performed. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by Haleon.

The investigator should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The date and time the subject signed the informed consent form will be captured in the eCRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the eCRF.

9.1.2 Demographics

The following demographic information will be recorded in the eCRF: year of birth, biological sex at birth and race.

Inclusion and exclusion criteria information will be documented in the eCRF.

9.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 1 year), including allergies or drug sensitivity, will be documented in the eCRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements, and herbal remedies, taken in the last 60 days and prior to signing the informed consent form, will be documented in the eCRF.

9.1.4 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical study. This will be documented in the eCRF.

9.2 Study Period

9.2.1 Baseline Period

The number of days each subject will actively engage with the study will be up to 28 days including baseline (See Appendix).

Study subjects who fulfil criteria and deemed suitable by the investigator for participation will be provided with the Actigraph wearable device which will measure aspects of functional mobility during the baseline period. The baseline period will last between 3 (minimum) and 7 days (maximum), to collect enough information on both subjective and objective aspects of mobility and sleep quality. End of baseline period will be considered day 0.

The baseline period will be variable and will depend on study subjects reaching ≥ 40 mm ≤70 mm of self-reported pain on the pain intensity visual analogue scale (VAS). Once the subject reaches any value at this level on the VAS scale, even for a single observation, the baseline period will be terminated, and study phase can commence.

At the end of the baseline period, the site staff will dispense the study product to the subject to take home and use throughout the study period as per label instructions. Before they start using the product, study subjects will complete the questionnaires to collect information on their baseline levels of quality of life and subjective perceptions of mobility and exercise capacity.

All medications taken during the 60 days prior to the screening visit and throughout the trial (other than study medication) will be recorded on the eCRF.

9.2.2 Days 1-21

The number of days each subject will actively engage with the study will vary according to the baseline measurements. Voltaren Gel use will be limited to 21 days, but study

subjects are allowed to stop using the product if they do not feel the need to continue using it (e.g., if the pain subsides). Study subjects will be told to use the products as per label instructions. Actigraph will collect mobility and sleep-related information continuously (24/7) throughout the study.

All questionnaires will be provided at pre-specified time-points during the study (please see schedule of activities table). Safety, adverse events, and use of concomitant medications will be monitored throughout the study. If a subject stops using the product before Day 21 (post baseline), they will be prompted to complete all relevant questionnaires before concluding the study.

The following assessments will be completed by subjects during the study period:

- Subjects will report any changes in health, concomitant medications, or non-drug treatments/procedures.
- Subjects will use Actigraph and complete additional QoL questions each day.
- Subjects will complete an eDiary to record product use each day.
- Subjects will report any adverse events.
- Subjects will report the end of product use and answer end of the study questions prior to exiting the study.

Subjects who do not use the product at all throughout the study will be considered as dropouts. Partial usage of the product across the treatment period (Day 7 to Day 21) is allowed to capture RWE usage of the product.

9.2.3 End of Treatment Period/End Of Study

Subjects will have the option to discontinue treatment at their discretion. The reasons for discontinuing treatment will be captured whenever possible.

Subjects may choose to discontinue treatment if they feel that their symptoms do not warrant further use of the study product.

Subjects who wish to continue to use the study product will be prompted to discontinue treatment after the end of the study (28 days) and seek advice from their general practitioner for further assessment and treatment on their condition if needed.

Subjects will also be informed that the study will end on Day 21 (or the day after the last treatment, if earlier than 21 days), and will be asked to fill in an exit survey and perform final urine pregnancy test .

At the end of the study (Day 28), Actigraph device and the allocated product (used and unused) for this clinical study, should be returned to the Haleon Clinical Supplies Department or CCI using the return instructions provided.

9.3 Diary Review

The eDiary should be reviewed at the end of Study, during Day 7,14 and 21 by the investigator, and periodically up to the discretion of investigator (remotely via telephone call or via email communications – this is up to the discretion of the site staff and the subject). Any subject comment captured in the eDiary which is considered an adverse event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarised in Adverse Event and Serious Adverse Events.

Any additional comments relating to medications/treatments provided in the eDiary will be reviewed by the investigator or medically qualified designee with the subject and investigator entered the eCRF as appropriate.

9.4 Study Conclusion

The Study Conclusion page of the eCRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the Haleon medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

9.5 Follow-up Visit/Phone Call

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

10 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

10.1 Screening Assessments

Subject enrolment will be determined based on the inclusion/exclusion criteria during screening.

10.2 Quality of Life Assessments

The following quality of life tools will be completed by subjects daily in the subject eDiary from receipt of product to study conclusion.

- WOMAC, NRS and EQ-5D-5L Questionnaire.
- QoL and Sleep/alertness Questionnaires.

10.3 Wearable Assessments

The following wearable assessments will be performed by Actigraph daily and will be correlated with QoL assessments from receipt of product to study conclusion.

- Moderate and Vigorous Physical Activity.
- Physical and sleep based activities.

10.4 Safety and Other Assessments

Subjects will report any adverse events throughout the study from consent to study conclusion.

Subjects will complete an eDiary to record product use each day.

Subjects will complete end of the study questions as outlined to them during consent.

The local investigator will record any relevant medical and surgical history, including allergies or drug sensitivity, and adverse events. The local investigator will also record use of any current medications/treatments, including prescription and non-prescription drugs, dietary supplements, and herbal remedies.

11 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study product or the study, or that caused the subject to discontinue the study product or study.

11.1 Definition of an Adverse Event (AE)

An AE is 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).

NOTE: 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).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after informed consent signing (prior to study product administration) even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred, or was necessary, the AE should be considered serious.
  - Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

11.3 Reporting Procedures

The investigator is responsible for detecting, documenting, and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the eCRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to Haleon in lieu of completion of the AE eCRF page/SAE form.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the eCRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

11.3.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the eCRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the AE eCRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the eCRF as well as on the form for collection of SAE information.

11.3.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE eCRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and Haleon assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the Single Case Processing mailbox (**Table 11-1**), , with a copy to the appropriate Haleon or CCI [redacted] Study Manager, with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available.

The initial report will be followed up with more information as relevant, or as requested by the study manager.

The Haleon Study Manager will be responsible for forwarding the SAE form to other Haleon personnel as appropriate.

The investigator (s) will be responsible for notifying the IRB/IEC of SAEs that occur during the study.

Table 11-1 Single Case Processing mailbox

United States	PPD
Americas (Non-US): Canada/Mexico/South & Latin America	PPD
EMEA: Europe, Middle East, Commonwealth of Independent State (CIS), Africa	PPD
Turkey	PPD
APAC countries (excluding Japan)	PPD
Japan	PPD

11.4 Evaluating Adverse Events

11.4.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined seriousness criteria as described in the definition of an SAE, NOT when it is rated as severe.

11.4.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE eCRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to Haleon. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to** Haleon**.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

11.5 Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by Haleon to elucidate as fully as possible the nature and/or causality of the SAE or AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE eCRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to Haleon within 24 hours of receipt of the information.

The investigator will submit any updated SAE data to Haleon within 24 hours.

11.6 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE eCRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

11.7 Pregnancy

11.7.1 Time Period for Collecting Pregnancy Information

Although study product use is not recommended during pregnancy, and this is an exclusion criterion for participating in the study, pregnancy test will be performed at Screening (site Visit 1) and End of Study (Visit 3) (See Schedule of Activities) and pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 1 day after last administration of study product.

Women of childbearing potential included in the study are advised to use an effective method of contraception from the time of screening and until 1 day after last administration of study product.

An effective method of contraception can achieve a failure rate less than 1% per year when used consistently and correctly. As per recommendations related to contraception and pregnancy testing in clinical trials (Clinical Trials Facilitation and Coordination Group CTFG 21/09/2020 Version 1.1), such methods include:

• combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)

• progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable, intrauterine device (IUD)

• intrauterine hormone-releasing system (IUS)

• surgical sterilisation (e.g., bilateral tubal occlusion)

• vasectomised partner

• sexual abstinence

11.7.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the Single Case Processing mailbox (**Table 11-1**), with copy to the appropriate Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the Single Case Processing mailbox at Haleon (**Table 11-1**), with copy to the appropriate Study Manager. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The investigator will record pregnancy information on the appropriate form and submit it to CCI within 24 hours of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to CCI Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

CCI will scan and email the pregnancy form to the Single Case Processing mailbox at Haleon (**Table 11-1**) with copy to the appropriate Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

11.8 Reporting Serious Adverse Events and Other Safety Issues to Regulatory Authorities/ Ethics Committees

All Suspected Unexpected Serious Adverse Reaction (SUSARs) that occur with the IMPs within or outside the concerned clinical trial, if required, will be reported by Haleon to Eudravigilance (EVCTM) in compliance with the timelines and standards for reporting SUSARs set out in the EU Clinical Trial Regulation 536/2014. Investigators will be informed about any safety profile changes and will receive SUSARs via Council for International Organizations of Medical Sciences (CIOMS) form or by periodic line-listings produced by Haleon.

Regarding regulations in force for pharmacovigilance, investigators must fulfil their obligations according to the law in force in their country, including reporting of (Serious) Adverse Events or any other information/listing as per their ECs/IRB requirement.

In addition to SUSARs, all unexpected events that might materially influence the benefit-risk assessment of the medicinal product will be performed and Ethics Committee will be notified as set out in EU Clinical Trial Regulation 536/2014.

11.9 Risks and benefits related to the participation in the clinical trial

11.9.1 Risks related to Voltaren gel

The Investigational Medicinal Product (IMP), Voltaren gel, is registered and marketed in countries concerned by the study. The IMP will be used in accordance with the indications, posology and safety product information approved.

Voltaren gel is contraindicated in the following circumstances:

- In patients with a known hypersensitivity to diclofenac or to any of the product excipients.
- In patients in whom asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- During the last trimester of pregnancy and during lactation/breastfeeding.

Special Warnings & Precautions for Use:

The possibility of experiencing systemic adverse events (those associated with the use of systemic forms of diclofenac) should be considered if Voltaren gel is used at a higher dosage or for a longer period of time than recommended.

Voltaren gel should be applied only to intact, non-diseased skin, and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes and should not be ingested. Voltaren Emugel can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

Interactions with other Medical Products and other Forms of Interaction:

Since systemic absorption of diclofenac from topical application is very low, interactions are unlikely.

Pregnancy & Lactation:

There are insufficient data on the use of diclofenac in pregnant women. Diclofenac should be used during the first two trimesters of pregnancy only if the expected benefit justifies the potential risk to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus

It is not known whether topical diclofenac is excreted in breast milk. Diclofenac should only be used during lactation if the expected benefit justifies the potential risk to the new-born. If there are compelling reasons for using it, it should not be applied to the breasts, nor should it be used at a higher dosage or for a longer period of time than recommended

Ability to perform tasks that require Judgement, Motor or Cognitive Skills:

Topical application of diclofenac has no influence on the ability to drive and use machines.

Adverse Reactions:

Adverse reactions are tabulated below by System Organ Class and frequency. The following convention has been utilised for the classification of undesirable effects: very common (≥ 1/10) common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 11-2 Adverse Reaction Frequency

MedDRA SOC	Adverse Reaction	Frequency
Infection and infestation	Rash pustular	Very rare
Immune system disorders	Angioedema, hypersensitivity (including urticaria)	Very rare
Respiratory, thoracic and mediastinal disorders	Asthma	Very rare
Skin and subcutaneous tissue disorders	Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus.	Common
	Dermatitis bullous	Rare
	Photosensitivity reaction	Very rare

Overdosage:

The low systemic absorption of topical diclofenac renders overdose unlikely. However undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if topical diclofenac is ingested. In the event of accidental ingestion, resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicines should be used.

11.9.2 Benefits

Participating in this clinical study offers patients several significant benefits:

Enhanced Understanding of Real-World Effectiveness:

Real World Evidence (RWE) studies, such as this one, provide valuable insights into how a product performs in everyday settings, reflecting a more accurate picture of its effectiveness in a diverse population. This study aims to evaluate the real-life impact of using Voltaren gel (diclofenac) on functional mobility and quality of life, ensuring that the findings are highly relevant to the typical consumer base.

Objective Measurement of Benefits:

The study will go beyond subjective assessments of benefits in the field of OA and Pain. Utilising research-grade wearable devices (Actigraph), the study will measure changes in functional mobility and quality of life aspects. This objective data collection allows for precise monitoring of the patient's progress, providing a clear and quantifiable understanding of how Voltaren gel influences daily activities and overall well-being.

Comprehensive Data Collection:

The study combines both objective and subjective assessments to offer a holistic view of the benefits of using Voltaren gel. This dual approach ensures a thorough evaluation, capturing the nuanced ways in which the gel improves functional mobility and quality of life, beyond just pain relief.

Personalised Health Insights:

Patients will receive detailed feedback on their mobility and quality of life, derived from both the wearable device data and subjective reports. This personalized information can help patients better understand their condition and the impact of the treatment, enabling more informed discussions with healthcare providers.

Contribution to Medical Knowledge:

By participating in this study, patients contribute to a broader understanding of how topical diclofenac can benefit individuals with osteoarthritis and other conditions causing pain and impaired mobility. The findings from this study could inform future treatment guidelines and improve care strategies for others with similar conditions.

Potential for Improved Quality of Life:

Given the established benefits of diclofenac in pain relief and the potential for enhanced mobility and daily functioning, patients in this study may experience substantial improvements in their quality of life. Improved mobility can lead to increased ability to engage in physical activities, better sleep, enhanced mood, and greater participation in daily activities, which collectively contribute to overall well-being.

Safety and Monitoring:

Participants in this study will be closely monitored, ensuring any adverse effects are promptly addressed. This level of attention can provide patients with a sense of security and immediate support, enhancing the overall treatment experience.

Participation in this study not only offers potential direct benefits to the patients in terms of improved mobility and quality of life but also contributes to the advancement of medical knowledge and the potential to benefit future patients with similar conditions. The comprehensive and personalised insights gained through this study can empower patients and enhance their treatment journey.

11.9.3 Risks/Benefits Evaluation

Diclofenac is a well-established NSAID that has analgesic and anti-inflammatory activities. Topical diclofenac has a wide and long-standing use for the symptomatic treatment of acute and chronic musculoskeletal conditions, including mild osteoarthritis of the knee and fingers.

In the European Economic Area (EEA), diclofenac diethylamine 1.16% gel and 2.32% gel (Voltaren Emulgel), were respectively first registered in 1985 in Switzerland and Romania, and in 2011 in Portugal. Since then, many topical diclofenac medicines, including gels, sprays, and patches, have been registered in the EEA countries. Furthermore, diclofenac sodium 1% gel has been approved in the US since 2007 for prescription use and since 2020 for over-the-counter use for the temporary pain relief of osteoarthritis.

The degree of scientific and clinical interest in the use of diclofenac diethylamine is reflected in the wealth of studies and publications, as well as the coherence of the scientific and clinical assessments. The topical application of diclofenac achieves therapeutically effective concentrations in the target tissues, whilst minimizing systemic exposure. Diclofenac preferentially distributes and persists in deep inflamed tissues, such as the joints. Pharmacokinetic studies have also demonstrated that diclofenac, when applied topically, penetrates the skin barrier to reach soft tissues, joints, and the synovial fluid in sufficiently high concentration to exert local therapeutic activity.

To minimise the risks for the participating subjects, inclusion and exclusion criteria have been carefully selected considering the approved safety product information of Voltaren gel. The study is a low-interventional clinical trial, and the product will be used as per the approved indications and posology.

During the study, the subjects will be monitored for any deterioration in general well-being, and they will be asked to report any adverse events, whether they occur during the study.

As sufficient information about the Investigational Medicinal Product is already available, no special safety investigations will be carried out during the clinical trial.

In summary, regular checks (3 visits) will be taken to mitigate potential risks and to ensure adequate safety of the subjects participating in this clinical trial.

After consideration of the risks and benefits, the performance of the clinical trial is considered ethically justifiable, as the expected future therapeutic benefits of the IMP appear to be greater than the risks to the subjects.

12 DATA MANAGEMENT

As used in this protocol, the term eCRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an eCRF, using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The source documents (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, dispensing records, recorded data from automated instruments) which contain the source of data recorded in the eCRF should be specified. The eCRF or e-Dairy can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

12.1 Case Report Form

For each subject who has given informed consent/assent the eCRF must be completed and signed by the investigator or authorized designee to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Management of clinical data will be performed in accordance with Third Party Biostatistics and Data Management (BDM) Vendor applicable standards and data cleaning procedures with oversight by Haleon to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or full birth date) is to be recorded in the eCRF or as part of the query text.

All eCRF pages should be completed during a subject assessment when the eCRF has been designated as the source. Data that is sourced elsewhere should be entered into the eCRF in an agreed upon timeframe between the Investigator and Sponsor.

Haleon will obtain and retain all eCRFs and associated study data as applicable at the completion of the study.

12.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the investigator.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary.

12.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the eCRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the eCRFs in accordance with the monitoring plan, to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the eCRFs, to raise manual queries as needed for site clarification or correction.

12.3 Processing Patient/Subject Reported Outcomes and Data Collection from Internet of Medical Things

Electronic Patient reported outcome (ePRO) data will be collected using electronic devices and transferred electronically to CRO and Haleon.

All ePRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the eCRF and/or DMS. ePROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or Haleon as required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by a member of the study team.

To protect the privacy of subjects, no personal information (including the subject's name or initials or birth date) is to be recorded on any ePRO that will be forwarded to Haleon or CCI

13 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

13.1 Sample Size Determination

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.

13.2 Populations for Analysis

- The enrolled population will include all subjects who meet the inclusion/exclusion criteria.
- The safety population will include all subjects who use study product at least once. Safety population will be used of safety variables.
- 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.

13.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior

to study analysis. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

All data extracted from Actigraph and subjective assessments may undergo visualisation, and graphs will be plotted wherever feasible. For instance, data pertaining to both the daily average number of steps taken and the daily average number of stairs climbed/descended will be presented in sets of charts, graphs, and heatmaps. This approach aims to enable a more thorough analysis, fostering a comprehensive understanding of intricate patterns, trends, and relationships embedded in the dataset. Further information will be provided in the statistical analysis plan (SAP).

13.3.1 Primary Analysis

Total study duration is 28 days, with primary analysis performed post baseline (baseline is from Day -7 to Day 0). 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.

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 21, inclusive. Any days beyond day 21 will be excluded from all summaries and analyses and will only be present in listed data.

A Mixed Model with Repeated Measures (MMRM) will be used to analyse the change from baseline in MVPA average minutes as the response variable. Subjects will be included as a random effect, and timepoint will be treated as a repeated measure within each subject. If data are found to be non-normal, an appropriate non-parametric test will be performed. If the parameter for the intercept (with compound symmetry structure between visits) is found to be statistically significant (p-value < 0.05), then the individual timepoints (with unstructured covariance structure between visits) will be added as a fixed effect and adjusted means for each timepoint will be presented. P-values and 95% confidence intervals (CIs) for the mean change from baseline in MVPA will be obtained and presented for each timepoint. Other than the global test for an overall change from baseline (i.e., intercept), there will be no other adjustment for multiplicity.

13.3.2 Secondary Analysis

For the secondary objective, functional mobility as measured through wearables and PRO, pain intensity assessed through NRS (daily assessment), activity-related pain and stiffness as measured in the WOMAC subscales for composite pain and composite stiffness will be analysed using the same MMRM as in the primary objective where the last observed daily value up to Day 0 will be used as the baseline value.

Correlations of quality of life will also be provided as it pertains to the following:

- Sleep/alertness: Karolinska Sleepiness Scale assessed 1x/day.

- Health-related quality of life: EQ-5D-5L.
- Change in the number of study subjects reporting that they feel more in control of their arthritis pain before and after Voltaren use.

13.3.3 Safety Analysis(es)

All AEs will be coded using MedDRA. AEs will be categorized as related, probable, unlikely, or unrelated by responsible authority prior to database lock. The number of AEs/SAEs and number of subjects with AEs/SAEs will be listed and tabulated.

13.3.4 Exploratory Analysis(es)

For the exploratory endpoints, correlations between pain relief, mobility, and quality of life indices will be measured throughout the trial. Additionally, the use of concomitant medications and any changes in use of pain relief medications will be recorded throughout the trial.
Time-to-pain relief will also be measured after use of the test product; this will be measured as the elapsed time from test product use to achieving sufficient pain relief to stop using the product and will be evaluated using Kaplan-Meier curves.

13.3.5 Exclusion of Data from Analysis

Any reasons for exclusion from an analysis population will be listed, if applicable.

13.3.6 Demographic and Baseline Characteristics

Age and other continuous demographic and baseline variables will be summarized using descriptive statistics such as mean, range, median and standard deviation. Gender and other categorical demographic and baseline variables will be summarized using frequency counts and percentages for the safety and mITT populations.

12.3.6 Study Drug/Product Compliance and Use of Other Therapies

13.3.6.1 Study Drug/Product Compliance

Compliance and product use will be monitored throughout the study via eDiary and data transfers from Actigraph by relevant study personnel (Site Staff, CRO and Sponsor study team).

Study product compliance will be tabulated and summarized for the safety population. Summaries will include a simple yes/no frequency (and percent) count at each timepoint.

13.3.6.2 Prior and Concomitant Medications

Concomitant medications taken during the study will be listed for the safety population.

13.3.7 Handling of Dropouts and Missing Data

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. Additional details will be provided in the data management plan and reporting and statistical analysis plan.

13.3.8 Interim Analysis

No interim analysis is planned for this study.

14 STUDY GOVERNANCE CONSIDERATIONS

14.1 Quality Control

In accordance with applicable regulations including GCP, and Haleon procedures, Haleon or designee (i.e., CCI) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Haleon requirements.

When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

Haleon or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at Haleon. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

14.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Haleon may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of

the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator will notify Haleon or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Haleon or its agents to prepare the study site for the inspection and will allow Haleon or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to Haleon or its agent. Before response submission to the regulatory authority, the investigator will provide Haleon or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

14.3 Regulatory and Ethical Considerations

14.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent and/or assent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Haleon prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Haleon in writing immediately after the implementation.

14.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements. The study will be conducted in compliance with the EU Clinical Trial Regulation 536/2014, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

14.3.3 Subject Information

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Haleon and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Haleon in order to de-identify study subjects.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Haleon will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

14.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved generic, pre-screening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

Haleon will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

14.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within Haleon a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in Haleon -sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Haleon should be informed immediately.

In addition, the investigator will inform Haleon immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol,of ICH GCP or of the EU Clinical Trial Regulation 536/2014 that the investigator becomes aware of.

In compliance with Article 52 of the EU Clinical Trial Regulation 536/2014, Haleon will notify the member states concerns at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

14.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins in accordance with applicable Haleon processes.

Haleon intends to make anonymized subject-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient/subject care according to local regulatory requirements. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

14.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Haleon site or other mutually agreeable location.

Haleon will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policy and as per the country specific regulatory requirements for disclosure.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge. Additionally, accordance with the EU Clinical Trial Regulation 536/2014 Annex IV (the publication policy of the trial data) the data will be uploaded to the CTIS database within one year after end of trial.

14.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a Haleon audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On eCRFs or other documents submitted to Haleon, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to Haleon, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator as per the signed contractual agreement, from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, Haleon standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between Haleon and the investigator. The investigator must notify Haleon of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

According to the POL-000-300 Haleon Global Records Retention Schedule, Haleon and the investigator shall archive the content of the clinical trial master file for at least 30 years after the end of the clinical trial.

14.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of Haleon. In addition, Haleon retains the right to discontinue development of product at any time. For multicentre studies (if applicable), this can occur at one or more or at all sites.

If a study is prematurely terminated, Haleon will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by Haleon, all study materials must be collected and all eCRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, Haleon should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favourable opinion of a study, the investigator should promptly notify the Haleon and provide Haleon with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the Haleon monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and Haleon Standard Operating Procedures.

15 REFERENCES

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16 APPENDICIES

16.1 ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Table 16.1 Abbreviations

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse event
ANOVA	Analysis of variance
COX	Cyclooxygenase
CI	Confidence Intervals
CRF	Case report form
EC	Ethics committee
eCRF	Electronic Case Report Form
ePRO	Electronic Patient reported outcome
EudraCT	European Clinical Trials Database
EU	European Union
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HSI	Human Subject Information
IB	Investigator's brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional review board
IRC	Internal review committee
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
mITT	modified Intent-To-Treat
MVPA	Moderate and Vigorous Physical Activity
N/A	Not applicable
NSAID(s)	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
QC	Quality control
QoL	Quality of Life
RWE	Real World Evidence
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
WOMAC	Western Ontario and McMaster Universities Arthritis Index
US	United States (Of America)

16.2 STUDY QUESTIONNAIRES

16.2.1 Western Ontario and McMaster Universities Arthritis Index (WOMAC) 5-point Likert scale example

Severity, on average, during the last 48 hours, of:

Pain

	None	Slight	Moderate	Severe	Extreme
Pain – Walking	☐	☐	☐	☐	☐
Pain – Stair climbing	☐	☐	☐	☐	☐
Pain – Nocturnal	☐	☐	☐	☐	☐
Pain – Rest	☐	☐	☐	☐	☐
Pain – Weightbearing	☐	☐	☐	☐	☐

Stiffness:

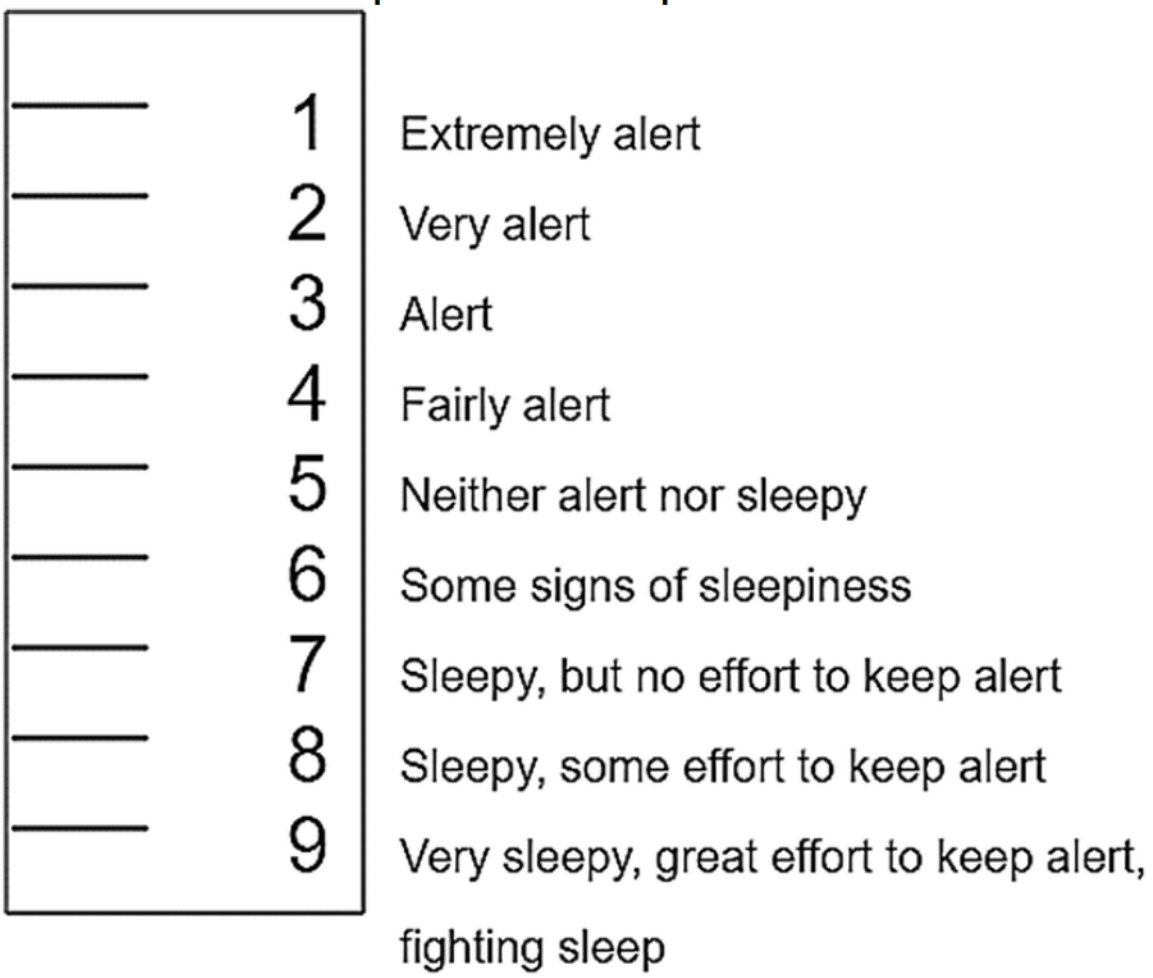
Morning Stiffness	☐	☐	☐	☐	☐
Stiffness occuring during the day	☐	☐	☐	☐	☐

Level of difficulty performing the following functions, on average, during the last 48 hours:

	None	Slight	Moderate	Severe	Extreme
Descending stairs	☐	☐	☐	☐	☐
Ascending stairs	☐	☐	☐	☐	☐
Rising from sitting	☐	☐	☐	☐	☐
Standing	☐	☐	☐	☐	☐
Bending to the floor	☐	☐	☐	☐	☐
Walking on flat	☐	☐	☐	☐	☐
Getting in/out of a car	☐	☐	☐	☐	☐
Going shopping	☐	☐	☐	☐	☐
Putting on socks	☐	☐	☐	☐	☐
Rising from bed	☐	☐	☐	☐	☐
Taking of socks	☐	☐	☐	☐	☐
Lying in bed	☐	☐	☐	☐	☐
Getting in/out of bath	☐	☐	☐	☐	☐
Sitting	☐	☐	☐	☐	☐
Getting on/off toilet	☐	☐	☐	☐	☐
Performing heavy domestic duties	☐	☐	☐	☐	☐
Performing light domestic duties	☐	☐	☐	☐	☐

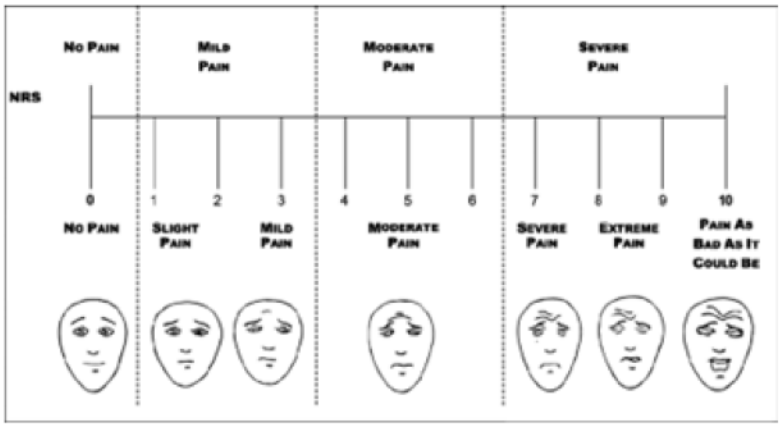
The WOMAC parameters are:
0 – none, 1 – slight, 2 – moderate, 3 – severe, 4 – extreme.
The index is out of a total of 96 possible points, with 0 being the best and 96 being the worst

16.2.2 Karolinska Sleepiness Scale Example

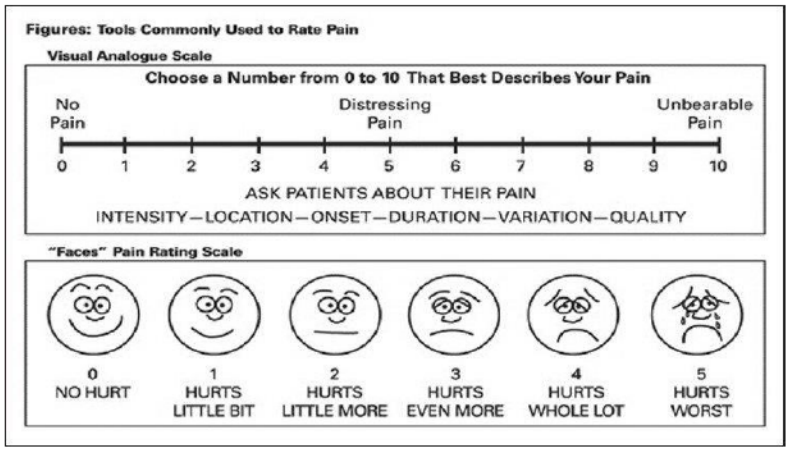


16.2.3 Self-Reported Pain Numerical Rating Scale and Visual Analogue Scale Examples

Numerical Rating Scale:



Visual Analogue Scale:



16.2.4 EQ-5D-5L Quality of Life Questionnaire example

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

16.3.1 End of the study questions

- **How would you rate your satisfaction with the Voltaren Gel you used?**

  Very Satisfied
  Satisfied
  Neutral
  Dissatisfied
  Very Dissatisfied
  Please explain why you chose Very Satisfied/Satisfied/Neutral/Dissatisfied/Very Dissatisfied?

- **Will you consider using Voltaren Gel for OA knee pain again?**

  Yes
  No
  Please explain why you would/would not use this product again.

After taking Voltaren Arthritis Pain Relieving gel:

- I find less discomfort ascending and descending stairs:

Strongly Agree
Agree
Neutral
Disagree
Strongly Disagree

16.4 ACTIGRAPH INFORMATION

Actigraph is ISO-13485:2016 certified, and the wearable technology is FDA 510(k) cleared Class II medical devices in the U.S. and adhere to regulatory standards worldwide. Further information on Actigraph certification can be found in the following links:

- https://theactigraph.com/compliance
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K181077

Information on how to train videos and frequently asked questions can be found on Actigraph tutorial part of the website: https://theactigraph.com/tutorials

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: PPD

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