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GlaxoSmithKline
Consumer Healthcare

CLINICAL PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Steady-State Pharmacokinetic and Disposition Study Characterizing Diclofenac's Plasma and Knee Exposure in Osteoarthritis Subjects Undergoing Scheduled Arthroplasty after Treatment with Diclofenac Diethylamine 2.32% Gel

Compound Name:	Diclofenac Diethylamine 2.32%
United States (US) Investigational New Drug (IND) Number:	N/A
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Sponsor information

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Document History

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Original protocol	12-Feb-2018	Not applicable (N/A)

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 and according to the current 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:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

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PROTOCOL SUMMARY

Purpose

The purpose of this study is to evaluate the exposure of diclofenac in the plasma and in the knee joint following topical administration of 2.32% diclofenac diethylamine (DDEA) gel (Voltarol 12 Hour Emulgel P 2.32% Gel in the UK, Voltaren Schmerzgel forte 23.2 mg/g gel in Germany) 4 g applied twice daily (b.i.d.) for 7 days.

Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To determine whether diclofenac penetrates into treated knee joint following repeated topical administration of diclofenac diethylamine 2.32% gel.	Diclofenac concentration in treated knee synovial tissue and synovial fluid after 7 days topical application of study treatment to the knee (12 hours after last application)
Secondary	
To evaluate the relative exposure of diclofenac in the knee joint vs. plasma.	Ratio between diclofenac concentration in treated knee synovial tissue and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application) Ratio between diclofenac concentration in treated knee synovial fluid and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application)
Exploratory	
To evaluate treatment effects upon COX-2 inhibition in the knee joint	PGE_2 levels in treated knee synovial tissue and synovial fluid after 7 days topical application of study treatment to the knee (12 hours after last application)
To evaluate treatment effects upon inflammatory cytokines in the knee joint	IL-6 and TNFα levels in treated knee synovial tissue and synovial fluid after 7 days topical application of study treatment to the knee (12 hours after last application)

Study Design

This will be a randomized, double-blind, multi-center, placebo-controlled clinical study investigating the concentration of topically applied diclofenac achieved in the knee joint synovial tissue and synovial fluid following b.i.d dosing for seven days.

The study will be performed in subjects diagnosed with osteoarthritis (OA) of the knee who are scheduled for arthroplasty of the knee as a treatment for their OA.

Approximately fifty (50) male and female OA subjects, who, at the time of screening, are ≥50 years old, will be randomized in a 2:1 ratio: two thirds will receive DDEA 2.32% gel treatment and one third placebo gel.

After providing informed consent to participate in the study the subjects will need to forego any NSAID or COX-2 treatment for at least 7 days prior to starting study treatment (Visit 2) in order to allow wash-out of existing therapy and thus avoiding confounding the effect of the study treatments. Dosing will be scheduled to commence seven days prior (at minimum) to the scheduled surgery and will occur twice a day following dosing instructions. If surgery is delayed dosing with study treatment can continue up to 14 days.

There will be 4 study center visits as follows:

Visit 1	Screening visit: Day -7 (Window: Day-10 to Day-7)
Visit 2	Baseline (randomization) visit: Morning of Day 1
Visit 3	Hospital admittance through to surgery and post-surgery: Evening of Day 7 through Day 8 (Surgery may be delayed by up to 7 days)
Visit 4	Final visit: Day 8 to Day 10 (Between recovery and discharge)

The subjects will be provided paracetamol as rescue medication, to be used up to a total daily dose of 4 g. Rescue medication will be available from the Screening Visit (Day -7) through to end of Day 7. Should the need arise for additional pain relief, the investigators will be allowed to prescribe codeine or tramadol. Postoperative analgesia will be handled according to the surgical center's pain management procedures.

The first dose of the study treatment is applied to the target knee during Visit 2 on Day 1 by a study nurse (or designee) at the study site. It will then be applied twice a day by a trained nurse (or designee) at the subject's home or other place of convenience commencing on the evening of Day 1 to allow for directly observed compliance, a record of drug applied and a check for concomitant medications and AEs. Subjects will be admitted to the unit on the day before the scheduled surgery (Day 7). The last dose of study treatment will be administered at the study site 12 hours (window -1/+3 hrs) prior to arthroplasty surgery.

Blood samples to measure diclofenac plasma concentrations will be taken as follows:

- One blood sample at baseline within one hour prior to administration of study treatment (Visit 2/Day 1)
- One blood sample within one hour prior to last dose of study treatment (Visit 3/Day 7)
- One blood sample between last dose of study treatment and commencement of surgery (at least 3 hours after dosing and more than 3 hours before surgery)
- One blood sample during surgery on Day 8 (between anaesthesia and completion of surgery)

The subjects will have a scheduled arthroplasty performed on their target knee (upon which the study treatment has been applied). During the surgical intervention synovial tissue and synovial fluid, to measure diclofenac concentration and PGE_2, IL-6 and TNFα levels, will be sampled as follows:

- Two (2) synovial tissue samples of approximately 2 to 3 cm^3 each
- Four (4) aliquots of 2.5-3 mL of synovial fluid

The following safety assessments will be conducted:

- Complete physical examination and vital signs at all study center visits.
- Electrocardiogram: 12-lead ECG at Screening visit, Pre-surgery visit and Final visit
- Standard clinical safety laboratory (biochemistry and hematology) at Screening visit, Pre-surgery and at Final visit

- AEs at all study visits and nurse's home visits

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally 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. Male and female subjects who, at the time of screening, are ≥ 50 years of age.
3. Subject has a diagnosis of OA of the knee requiring arthroplasty and is scheduled for single knee arthroplasty, with radiographic evidence within last 6 months confirming Kellgren Lawrence grade of 2 or more.
4. Subject is in general good physical health and deemed fit for surgery, as judged by the investigator and no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, respiratory rate and temperature measurement, 12-lead ECG or clinical laboratory tests.
5. Body Mass Index (BMI) of 17.5 to less than 40 kg/m2; and a total body weight >50 kg (110 lbs).
6. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
7. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 21 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in Section 4.4.4.

Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are GSK employees directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s) within one month prior to study entry and/or during study participation.
3. 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, would make the subject inappropriate for entry into this study.
4. Pregnant female subjects.
5. Breastfeeding female subjects.
6. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. Subjects in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
8. Subjects whose skin around the knee is broken, diseased or has skin wounds or open injuries.
9. Unwilling or unable to comply with the lifestyle guidelines described in this protocol (Section 4.4 Lifestyle Guidelines) or investigator instructions.
10. Use of prescription or nonprescription drugs (unless deemed necessary by investigator), NSAIDs, COX-2 inhibitors and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment and during the study. Specifically if, during the washout period or the treatment period, the subject is unwilling to avoid the use of any topical or systemic

analgesic or anti-inflammatory treatments other than the study medication, the rescue medication, and if needed codeine or tramadol.

11. Use of one or more of the following treatments prior to the screening visit or between screening and baseline visit:
    - any topical NSAID treatment between screening and baseline visit
    - any intra-articular or peri-articular procedures or injections in either knee within the previous 3 months,
    - any systemic treatment with corticosteroids within the previous 6 weeks (topical treatments with corticosteroids not related to either knee are permitted up to screening visit),
    - any chondroprotectant or disease-modifying OA drugs, such as glucosamine or chondroitin sulfate, unless dose was stable over the previous month and will be maintained throughout the study,
    - any systemic anti-inflammatory or analgesic drugs at screening if 5 times their elimination half-time exceeds 7 days (i.e., if half-life > 33.6 h),
    - anticoagulants such as warfarin or heparin in the preceding week or antiaggregants within the previous month other than aspirin at stable low doses started at least one month before randomization and kept at a constant dose throughout the study or anticoagulant therapy for surgery,
    - any other investigational drugs within the previous month or 5 half lives preceding the first dose of investigational product (whichever is longer).
12. A positive urine drug screen during Screening (Day -7).
13. Any condition possibly affecting drug absorption (e.g., gastrectomy).
14. History of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.
15. Subjects who have previously been enrolled in this study.

Study Treatments:

Arm	Treatment
Active Treatment	2.32% DDEA gel applied to OA knee twice a day for 7 days*
Placebo Control	Placebo gel applied to OA knee twice a day for 7 days*

*up to 14 days if surgery is delayed

Statistical Considerations and Data Analyses

Sample Size Determination

A formal estimation of sample size was not carried out. The sample size selected (approximately 30 subjects on active, 15 subjects on placebo control) for the present study is in general agreement with similar studies (Benito 2005, Gallelli 2013, Gallelli 2012, Alvarez-Soria 2006, Fowler 1983, Efe 2014) and is deemed adequate to provide information on diclofenac concentration(s) in treated knee synovial tissue and synovial fluid.

Approximately 50 subjects will be randomized to account for 10% dropout and ensure evaluable data for 45 subjects who underwent the surgery.

Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical reporting analysis plan (RAP), which will be written following finalization of the protocol and prior to study unblinding.

Definition of Analysis Populations

The safety population will include all subjects who are randomized and have received at least one dose of investigational product.

The analysable population will consist of all subjects included in the safety population, who completed the surgery and have evaluable synovial tissue or synovial fluid sample.

The Per-Protocol (PP) population includes all subjects from the analysable population who do not have any major protocol deviations that could confound the interpretation of analyses conducted on the analysable population. Protocol deviations that would exclude subjects from the PP population are defined in Section 10.2.2.

The breakdown of subjects into the analysis sets will be presented.

Exclusion of Data from Analysis

All evaluable data will be included in the analysis.

Protocol deviations that would exclude subjects from the PP population may include (but are not limited to) the following:

- Major deviations in synovial tissue and synovial fluid sampling
- Subjects with poor compliance with study treatment
- Subjects taking prohibited medication or treatment during the study which is felt to affect the assessment of synovial tissue and synovial fluid samples.

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting and documented in the RAP prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

Demographic and Baseline Characteristics

Demographic and other baseline data will be presented using descriptive statistics and will be listed.

Categorical variables will be summarized by the number and percentage of subjects with each relevant characteristic. Continuous variables will be summarized by calculating the mean, standard deviation, median, minimum and maximum.

Study Drug/Product Compliance and Use of Other Therapies

Study Drug/Product Compliance

Compliance with study drug will be summarised in the analysable population as the number of subjects with a minimum of 12 applications before surgery.

Prior and Concomitant Medications

Other medications will be listed in the safety population. Concomitant medications will be summarized by preferred term, and the number and percentage of subjects who took any concomitant medication, will be presented.

Other Therapy/Rescue Medication (if applicable)

The use of rescue medication (number of subjects that used rescue medication, number of days on rescue medication and total dose of paracetamol taken) will be presented by treatment group for the analysable population.

Primary Analysis(es)

Evaluation Criteria

The success criterion of this study is that diclofenac can be detected within the treated knee synovial tissue or synovial fluid after 7 days treatment.

Analysis

The primary endpoints are diclofenac concentrations in treated knee synovial tissue and synovial fluid at 12 hours after last administration.

Synovial tissue and synovial fluid diclofenac concentrations will be summarized descriptively by treatment group in both the arithmetic and the logarithmic scale. The tables will present the proportion of subjects with values above the limit of quantification (LOQ) with its two-sided 95% confidence interval. The mean, SD, min, P10, Q1, median, Q3, P90, max will be calculated after replacing values below the LOQ by LOQ/2. The geometric mean will also be calculated with a two-sided 95% confidence interval assuming data on the logarithmic scale are normally distributed. Boxplots by treatment group will be produced on the original data.

The analysis will be performed on the analysable population.

Secondary Analysis(es)

Evaluation Criteria

The secondary objective is to evaluate the relative exposure of diclofenac in the knee joint vs. plasma.

Analysis

The secondary endpoints are

- Ratio between diclofenac concentration in treated knee synovial tissue and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application)
- Ratio between diclofenac concentration in treated knee synovial fluid and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application)

Following the same approach as for the primary endpoints, the ratios between diclofenac concentration in synovial tissue / fluid and diclofenac plasma concentration (last sample taken during surgery) will be summarized descriptively by treatment group in both the arithmetic and the logarithmic scale. Geometric means will be calculated with two-sided 95% confidence intervals. Boxplots by treatment group will be produced.

The analysis will be performed on the analysable population.

Safety Analysis(es)

Safety variables will be summarized on the safety population.

Exposure to study drug (number of applications, total weight of gel used) will be summarized by treatment group.

Treatment Emergent adverse events (TEAE, i.e. AEs that start or worsen after first study treatment administration) will be summarized by presenting, for each treatment group, the number and percentage of subjects having any TEAE, any TEAE in each MedDRA primary System Organ Class (SOC) and having each individual TEAE (using MedDRA preferred term). This will be done separately for all TEAEs and for TEAEs that are suspected to be drug-related. All TEAEs will also be tabulated in corresponding fashion by severity. Any other information collected (e.g. action taken, duration, outcome, seriousness) will be listed as appropriate.

All adverse events (prior to treatment and treatment emergent) will be listed.

Chemistry and hematology results at screening, Visit 3 and at Visit 4 will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group. Shift tables (between baseline and Visit 3, between Visit 3 and Visit 4) will also be presented. Laboratory normal ranges and all laboratory test results will be listed.

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate) recorded at Visit 3 and changes in vital signs from Visit 2 (baseline) to Visit 3 will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group. Vital signs at each assessment will also be listed.

ECG results at Visit 3 and Visit 4 will be summarised.

Other Analysis(es)

Evaluation Criteria

The success criteria for exploratory objectives are that

- diclofenac reduces PGE_2 levels in treated knee synovial tissue or synovial fluid after 7 days topical administration to the knee compared to placebo gel
- diclofenac reduces levels of inflammatory cytokines i.e. TNF_α and IL-6 associated with OA in treated knee synovial tissue and synovial fluid after 7 days topical administration to the knee compared to placebo gel

Analysis

The exploratory endpoints are

- PGE_2 levels in treated knee synovial tissue and synovial fluid after 7 days topical administration to the knee (12 hours after last application)
- IL-6 and TNF_α levels in treated knee synovial tissue and synovial fluid after 7 days topical administration to the knee (12 hours after last application)

PGE_2 and inflammatory cytokines levels will be summarized descriptively in both the arithmetic and the logarithmic scale.

For each endpoint, the success criterion will be addressed by a two-sided test for superiority at level alpha=0.05 in an exploratory manner. Log-transformed mean levels will be compared between treatment groups using an analysis of variance including treatment as a fixed effect. The two-sided 95% confidence interval for the ratio of geometric means on the original scale will be derived by back-transforming the confidence interval for the difference between treatment groups on the log-transformed scale obtained from the analysis.

The analysis will be performed on the analysable population.

Diclofenac plasma concentrations will also be summarized on the analysable population by calculating the mean, standard deviation, median, minimum and maximum for the following timepoints: Visit 2

(baseline), Visit 3 (pre-dose), Visit 3 (sample taken between last application and surgery) Visit 3 (last sample taken during surgery).

Handling of Dropouts and Missing Data

Missing data will not be imputed. All evaluable parameters after 7 days from subjects in the analysable population will be used in the analysis of primary, secondary and exploratory endpoints. Values that are below the limit of quantification (BLOQ) will be replaced by LOQ/2.

SCHEDULE OF ACTIVITIES

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

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

Table 0-1 Schedule of Activities

Procedure/Assessment	**Visit 1** **Screening**	**Visit 2** **Baseline**	*At Home*	**Visit 3 Inpatient** **Pre-Surgery**	**Surgery**	**Visit 4 Inpatient** **Follow-up**
Study Day	**Day -7 (Day -10 to Day -7)**	**Day 1**	*Day 1 (pm) –Day 7 (am)*	**Day 7 (pm)**	**Day 8[a]**	**Day 8-10**
Informed consent	X					
Inclusion/Exclusion criteria	X	X[b]				
Demographics, Height, Weight	X					
Medical history and Prior medications	X	X[c]				
Randomization		X				
Full Physical Exam and Vital signs (BP, PR, RR, temperature)	X	X		X[k]		X
12-lead ECG[d]	X			X[k]		X
Safety Labs	X			X[k]		X
Urine drug test	X					
Urine pregnancy test	X	X				
Dispensing of rescue medication	X					
Collection of rescue medication				X		
Dispensing of study medication		X				
Collection of study medication				X		
PK blood draw[e]		X		X[f]	X[f]	

Procedure/Assessment	**Visit 1** **Screening**	**Visit 2** **Baseline**	*At Home*	**Visit 3 Inpatient** **Pre-Surgery**	**Surgery**	**Visit 4 Inpatient** **Follow-up**
Study Day	**Day -7 (Day -10 to Day -7)**	**Day 1**	*Day 1 (pm) –Day 7 (am)*	**Day 7 (pm)**	**Day 8[a]**	**Day 8-10**
Study Treatment Dose am[g]		X[h]	X			
Study Treatment Dose pm[g]			X	X		
TKR Surgery and sampling of synovial tissue and synovial fluid[i]					X	
Concomitant Treatments and Use of Rescue Medication		X	→	→	→	X
Adverse Events[j]	X	→	→	→	→	X
Study conclusion						X

[a] Day 8 or day of surgery assuming surgery is not delayed by more than 7 days

[b] Confirmation of inclusion and exclusion criteria

[c] Confirmation of medical history and prior medications

[d] Abbreviations: → = ongoing/continuous event; ECG = electrocardiogram, BP = blood pressure, PR = pulse rate, PK = pharmacokinetics, PD = pharmacodynamics, RR = respiratory rate, TKR = total knee replacement, am = morning (midnight to midday), pm = afternoon/evening (midday to midnight)

[e] Five milliliters (5 mL) of blood will be sampled at each time point

[f] One PK sample will be taken prior to last dose on Day 7. Two PK samples will be taken after administration of the last dose: one sample prior to surgery and one sample during surgery

[g] Doses should occur at least 8 hours apart and twice per day

[h] The first dose of study treatment will be applied after washout, at the clinic, at Visit 2. It will be administered by a study nurse at the study site, following baseline assessments.

[l] For PK and PD biomarkers

[j] Adverse events will be recorded from the signing of informed consent.

[k]Will take place between final dosing with study treatment and prior to surgery

1 INTRODUCTION

The purpose of this study is to evaluate the exposure of diclofenac in the plasma and in the knee joint following topical administration of 2.32% diclofenac diethylamine (DDEA) gel (Voltarol 12 Hour Emulgel P 2.32% Gel in the UK, Voltaren Schmerzgel forte 23.2 mg/g gel in Germany) 4 g applied twice daily (b.i.d.) for 7 days.

1.1 Mechanism of Action/Indication

Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with pronounced effects in the relief of pain, inflammation and increased temperature due to fever. Diclofenac acts through the inhibition of prostaglandin synthesis caused by blocking the enzyme cyclo-oxygenase 2 (COX-2). Inhibition of prostaglandin (PG) synthesis is the primary mechanism of action of diclofenac (Gan 2010).

The Indication (Global Data Sheet, Topical Diclofenac 2017) for DDEA 2.32% gel is:

"For the relief of pain, inflammation and swelling in:

- Soft-tissue injuries: trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains, bruises and backache (sports injuries);
- Localised forms of soft tissue rheumatism: tendonitis (e.g. tennis elbow), bursitis, shoulder-hand syndrome and periarthropathy.

For the relief of pain of non-serious arthritis of the knee or fingers."

1.2 Background and Rationale

Topical diclofenac products are well established globally for the treatment of pain and inflammation due to acute trauma as well as for the relief of pain associated with non-serious osteoarthritis (OA) of the peripheral joints e.g. knee and fingers. The originator product DDEA 1.16% gel (Voltarol Emulgel in the UK) was first registered in 1985 in Switzerland and Romania for use at a dose of 2-4 g applied three to four times daily and is currently registered in over 130 countries of which over 80 countries market this product as over-the-counter (OTC).

Topically administered 2.32% DDEA gel for use at a dose of 2-4 g applied twice daily (b.i.d.) was first approved in 2011 in Portugal as a line extension to DDEA 1.16% gel and is now registered in 72 countries and is marketed in approximately 43 countries. It is approved with OTC status in 66 countries.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

Unlike a tablet version of diclofenac, the topical formulations are administered onto the skin and diclofenac then moves through the skin to the local site of action and exerts its therapeutic effect. Diclofenac must therefore penetrate through the skin and then permeate through tissue in order to reach its site of action - primarily soft tissue (acute trauma indication) and synovial joints (OA indication).

DDEA 1.16% and 2.32% gels have demonstrated in clinical studies to be effective and well tolerated in providing relief of pain from several conditions (Global Data Sheet, Topical Diclofenac 2017).

However, there are sparse clinical data on the pharmacology of topically applied diclofenac that underpins the clinical efficacy data. Diclofenac is able to penetrate through the skin; the degree of penetration is determined by the specific composition of the formulation and by the pharmaceutical form (Hagen and Baker 2017). Far less information is available about the fate of the drug after skin penetration, namely:

- how diclofenac moves through to the site of action in the knee joint in OA
- the influence of systemic circulation
- the amount needed in the joint for pharmacological activity and hence efficacy.

The pharmacology of diclofenac in soft tissue and the knee has been characterized primarily by microdialysis and by arthroplasty (total knee replacement, TKR), respectively (Benito 2005) (Gallelli 2013) (Gallelli 2012) (Alvarez-Soria 2006) (Fowler 1983) (Efe 2014) (Liauw 1984). The greatest proportion of these studies was in the knee following oral administration of diclofenac tablet investigated during arthroplasty. Very few studies have been performed using topically applied diclofenac and no study with the DDEA 2.32% gel product.

Oral diclofenac effectiveness data from arthroplasty indicates a dose dependency and a relationship with diclofenac levels in the synovium. Diclofenac inhibits the COX-2 enzyme and subsequently decreases levels of prostaglandin E2 (PGE_2) in the knee following a concentration-response relationship with diclofenac levels in the synovium (Hagen and Baker 2017).

DDEA 2.32% gel is not indicated for severe OA, and the current study is not collecting efficacy data; the study is using arthroplasty as a model to evaluate the exposure and bioactivity of diclofenac in the plasma and in the knee joint following topical administration of the gel.

1.2.1 Relevant non-clinical data

The penetration of topically administered diclofenac into the treated knee has been investigated in the minipig (Wible 2014 and CCI [redacted]). These investigations demonstrated that topically administered diclofenac penetrates into the treated knee and that the degree of penetration is formulation dependent.

The GSK study evaluated diclofenac formulations including a twice daily DDEA 2.32% gel. (a close mimic of the marketed product). The study evaluated diclofenac in the tissues within and surrounding the treated hind knee and the contralateral untreated hind knees of the minipig following 7 days of twice daily dosing. Additionally, the diclofenac levels in the knee were assessed against their ability to inhibit stimulated PGE_2 production. The DDEA 2.32% gel penetrated into the treated knee causing concentration dependent inhibition of PGE_2. This study demonstrated that diclofenac containing products, when applied topically, can deliver diclofenac into the treated knee and act in a concentration dependent manner.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to determine whether diclofenac penetrates into the treated knee joint following repeated topical administration of diclofenac diethylamine 2.32% gel.

The primary, secondary and exploratory objectives and their respective endpoints are described in Table 2-1.

Table 2-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To determine whether diclofenac penetrates into treated knee joint following repeated topical administration of diclofenac diethylamine 2.32% gel.	Diclofenac concentration in treated knee synovial tissue and synovial fluid after 7 days topical application of study treatment to the knee (12 hours after last application)
Secondary	
To evaluate the relative exposure of diclofenac in the knee joint vs. plasma.	Ratio between diclofenac concentration in treated knee synovial tissue and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application) Ratio between diclofenac concentration in treated knee synovial fluid and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application)
Exploratory	
To evaluate treatment effects upon COX-2 inhibition in the knee joint	PGE_2 levels in treated knee synovial tissue and synovial fluid after 7 days topical application of study treatment to the knee (12 hours after last application)
To evaluate treatment effects upon inflammatory cytokines in the knee joint	IL-6 and TNFα levels in treated knee synovial tissue and synovial fluid after 7 days topical application of study treatment to the knee (12 hours after last application)

This study will be considered to be positive if the primary objective is met; i.e. that diclofenac is detected in the treated knee synovial tissue or synovial fluid after 7 days of topical treatment with DDEA 2.32% gel.

3 STUDY DESIGN AND SUBJECT POPULATION

This will be a randomized, double-blind, multi-center, placebo-controlled clinical study investigating the concentration of topically applied diclofenac achieved in the knee joint synovial tissue and synovial fluid following b.i.d dosing for seven days.

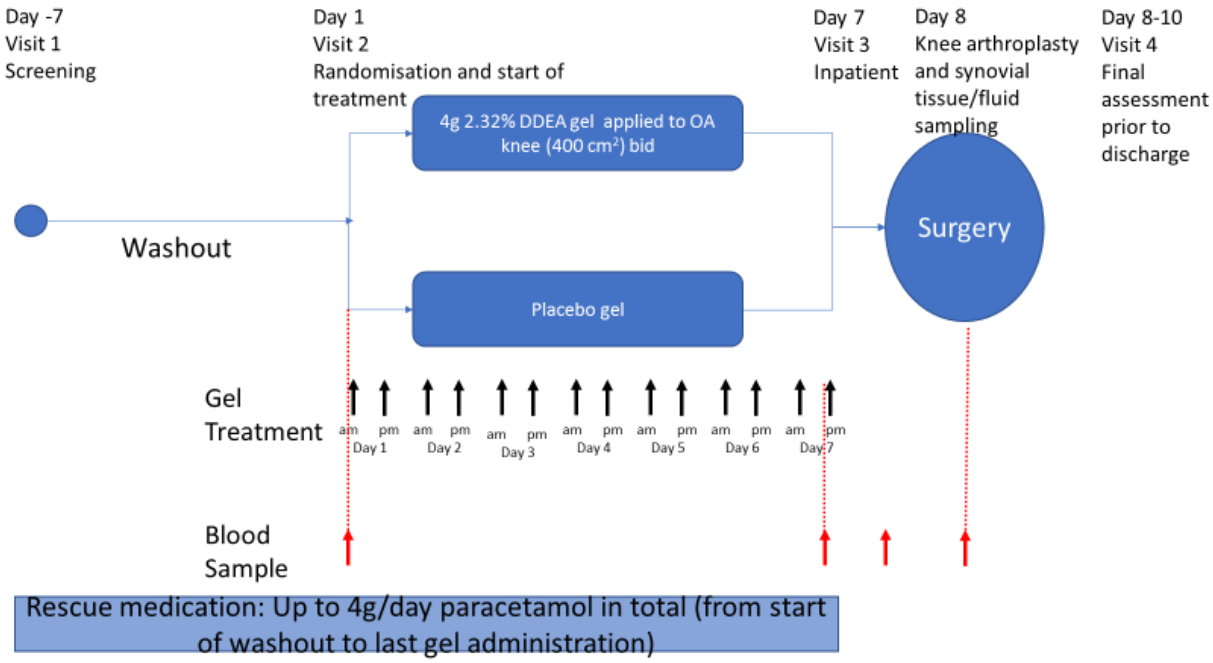
The study will be performed in subjects diagnosed with OA of the knee who are scheduled for arthroplasty of the knee as a treatment for their OA.

Approximately fifty (50) male and female OA subjects, who, at the time of screening, are ≥50 years old, will be randomized in a 2:1 ratio: two thirds will receive DDEA 2.32% gel treatment and one third placebo gel.

After providing informed consent to participate in the study the subjects will need to forego any NSAID or COX-2 treatment for at least 7 days prior to starting study treatment (Visit 2) in order to allow wash-out of existing therapy and thus avoiding confounding the effect of the study treatments. Dosing will be scheduled to commence seven days prior (at minimum) to the scheduled surgery and will occur twice a day following dosing instructions. If surgery is delayed dosing with study treatment can continue up to 14 days as per maximum dose duration in the UK SmPC.

A schematic of the study design is provided in Figure 3-1.

Figure 3-1 A schematic of the study design



There will be 4 study center visits as follows:

Visit 1	Screening visit: Day -7 (Window: Day-10 to Day-7)
Visit 2	Baseline (randomization) visit: Morning of Day 1
Visit 3	Hospital admittance through to surgery and post-surgery: Evening of Day 7 through Day 8 (Surgery may be delayed by up to 7 days)
Visit 4	Final visit: Day 8 to Day 10 (Between recovery and discharge)

Steady state for diclofenac is achieved by 7 days of dosing. Pharmacokinetic and exploratory marker sampling is to occur during surgery 12 hours after the last dose of study treatment, representing steady state of diclofenac. In the case where surgery is delayed, dosing with study treatment may extend beyond 7 days up to 14 days. In these cases, pharmacokinetic and exploratory marker sampling will still occur during surgery 12 hours after the last dose of study treatment as these points in time are still representative of diclofenac steady state and will be included in the analysis of the relevant endpoints

Table 3-1 Treatment arms for the study

Arm	Treatment	Surgery time
Active Treatment	2.32% DDEA gel applied to OA knee twice a day for 7 days*	12 hours (window -1/+3 hours) after last gel application
Placebo Control	Placebo gel applied to OA knee twice a day for 7 days*	12 hours (window -1/+3 hours) after last gel application

*up to 14 days if surgery is delayed

The study will include one active treatment arm and one placebo control arm (Table 3-1).

In the treatment arm, DDEA 2.32% gel will be applied to the knee planned for arthroplasty surgery (target knee). If the subject has bilateral knee OA, the treatment will be applied to the knee planned for surgery only and not to the contralateral knee. A placebo control arm is included to facilitate bioactivity comparisons. In the placebo control arm a placebo gel will be applied in a similar manner as the DDEA 2.32% gel on the knee planned for surgery (target knee).

A placebo control group was chosen to enable the evaluation of diclofenac on PGE_2, IL-6 and TNFα levels – providing a baseline comparator group. This will provide context on the bioactivity associated with the diclofenac levels achieved. Subjects will have full access to paracetamol rescue and non-NSAID analgesia. The taking of synovial fluid and tissue does not represent an increased degree of intervention over that experienced with the scheduled surgery.

The subjects will be provided paracetamol as rescue medication, to be used up to a total daily dose of 4 g. Rescue medication will be available from the Screening Visit (Day -7) through to

end of Day 7. Should the need arise for additional pain relief, the investigators will be allowed to prescribe codeine or tramadol. Postoperative analgesia will be handled according to the surgical center's pain management procedures.

The first dose of the study treatment is applied to the target knee during Visit 2 on Day 1 by a study nurse (or designee) at the study site. It will then be applied twice a day by a trained nurse (or designee) at the subject's home or other place of convenience commencing on the evening of Day 1 to allow for directly observed compliance, a record of drug applied and a check for concomitant medications and AEs. Subjects will be admitted to the unit on the day before the scheduled surgery (Day 7). The last dose of study treatment will be administered at the study site 12 hours (window -1/+3 hrs) prior to arthroplasty surgery. Additional activities/procedures may be required in the undertaking of the arthroplasty. Unless they fall within the details of this protocol, laboratory manual or pharmacy manual, they are outside the scope of this study.

Blood samples to measure diclofenac plasma concentrations will be taken as follows:

- One blood sample at baseline within one hour prior to administration of study treatment (Visit 2/Day 1)
- One blood sample within one hour prior to last dose of study treatment (Visit 3/Day 7)
- One blood sample between last dose of study treatment and commencement of surgery (at least 3 hours after dosing and more than 3 hours before surgery)
- One blood sample during surgery on Day 8 (between anaesthesia and completion of surgery)

The subjects will have a scheduled arthroplasty performed on their target knee (upon which the study treatment has been applied). During the surgical intervention synovial tissue and synovial fluid will be sampled as follows:

- Two (2) synovial tissue samples of approximately 2 to 3 cm^3 each
- Four (4) aliquots of 2.5-3 mL of synovial fluid

The surgical procedure will be performed according to the site's standard process. Sampling of the tissue and fluid will occur using clean equipment not used previously for surgery. This is to avoid contamination of the samples with blood. All sample handling details will be described in the Laboratory Study Manual.

The following safety assessments will be conducted:

- Complete physical examination and vital signs at all study center visits.
- Electrocardiogram: 12-lead ECG at Screening visit, Pre-surgery visit and Final visit
- Standard clinical safety laboratory (biochemistry and hematology) at Screening visit, Pre-surgery and at Final visit
- AEs at all study visits and nurse's home visits

4 SUBJECT SELECTION

This study can fulfill 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 nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol. Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally 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. Male and female subjects who, at the time of screening, are ≥ 50 years of age.
3. Subject has a diagnosis of OA of the knee requiring arthroplasty and is scheduled for single knee arthroplasty, with radiographic evidence within last 6 months confirming Kellgren Lawrence grade of 2 or more.
4. Subject is in general good physical health and deemed fit for surgery, as judged by the investigator and no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, respiratory rate and temperature measurement, 12-lead ECG or clinical laboratory tests.
5. Body Mass Index (BMI) of 17.5 to less than 40 kg/m2; and a total body weight >50 kg (110 lbs).
6. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
7. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 21 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in Section 4.4.4.

4.2 Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are GSK employees directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s) within one month prior to study entry and/or during study participation.

3. 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, would make the subject inappropriate for entry into this study.
4. Pregnant female subjects.
5. Breastfeeding female subjects.
6. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. Subjects in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
8. Subjects whose skin around the knee is broken, diseased or has skin wounds or open injuries.
9. Unwilling or unable to comply with the lifestyle guidelines described in this protocol (Section 4.4 Lifestyle Guidelines) or investigator instructions.
10. Use of prescription or nonprescription drugs (unless deemed necessary by investigator), NSAIDs, COX-2 inhibitors and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment and during the study. Specifically if, during the washout period or the treatment period, the subject is unwilling to avoid the use of any topical or systemic analgesic or anti-inflammatory treatments other than the study medication, the rescue medication, and if needed codeine or tramadol.
11. Use of one or more of the following treatments prior to the screening visit or between screening and baseline visit:
    - any topical NSAID treatment between screening and baseline visit
    - any intra-articular or peri-articular procedures or injections in either knee within the previous 3 months,
    - any systemic treatment with corticosteroids within the previous 6 weeks (topical treatments with corticosteroids not related to either knee are permitted up to screening visit),
    - any chondroprotectant or disease-modifying OA drugs, such as glucosamine or chondroitin sulfate, unless dose was stable over the previous month and will be maintained throughout the study,
    - any systemic anti-inflammatory or analgesic drugs at screening if 5 times their elimination half-time exceeds 7 days (i.e., if half-life > 33.6 h),
    - anticoagulants such as warfarin or heparin in the preceding week or antiaggregants within the previous month other than aspirin at stable low doses started at least one month before randomization and kept at a constant dose throughout the study or anticoagulant therapy for surgery,

- any other investigational drugs within the previous month or 5 half lives preceding the first dose of investigational product (whichever is longer).

12. A positive urine drug screen during Screening (Day -7).
13. Any condition possibly affecting drug absorption (e.g., gastrectomy).
14. History of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.
15. Subjects who have previously been enrolled in this study.

4.3 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

4.4 Lifestyle Guidelines

4.4.1 Meals and Dietary Restrictions

No specific meal or dietary restriction is required for the study. Subjects will follow the perioperative guidance with respect to meals and dietary restrictions as provided by the surgical center. Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations

4.4.2 Alcohol, Caffeine and Tobacco

Subjects will follow the perioperative guidance with respect to alcohol and caffeine intake and use of tobacco- or nicotine containing products as provided by the surgical center.

4.4.3 Activity

Subjects will follow the perioperative guidance with respect to activity as provided by the surgical center.

4.4.4 Contraception

Female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period (onwards from screening) and for at least 21 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her

designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

1. Established use of oral, inserted, injected, transdermal, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness as deemed appropriate by the investigator.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository).
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female who meets the criteria for non-childbearing potential as described below.
   Female subjects of non-childbearing potential must meet at least one of the following criteria:
   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;
   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   c. Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include screening number, date of screening, demography (gender, year of birth, age), screen failure details (e.g., withdrawal of consent), eligibility criteria, and any serious adverse events. Screening failures will be replaced in the recruitment schedule until the required number of subjects are randomized.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

4.6 Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

The contact number can be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol identifiers, subject study numbers, contact information for the investigational site, and contact details in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem identified from the subject's healthcare professional other than the investigator.

5 STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization 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 (ICH E6 1.33).

5.1 Blinding and Allocation to Treatment/Randomization

At Visit 2, participants who fulfill all the inclusion criteria and none of the exclusion criteria will be assigned a unique randomization number in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the two arms of the study according to the randomization schedule generated prior to the study by the Statistics Department at PPD. These randomization numbers are linked to the two treatment arms, which in turn are linked to container (kit) numbers. A separate container list will be produced by the Statistics Department at PPD. Subjects will be randomized using an interactive response technology system and container numbers will be provided by the system.

Subjects will be randomized in a 2:1 ratio: approximately two thirds will receive DDEA 2.32% gel treatment and one third placebo gel. Consecutive blocks of randomization numbers will be assigned to individual centers in order to stratify the randomization by center.

This is a double-blind study. The subjects, investigators and site staff, study statistician and other employees of the sponsor and vendors acting on behalf of the sponsor who may influence study outcomes will be blinded to the treatment allocation of subjects. The placebo gel and the active gel will be identical in packaging, labeling, odor, schedule of administration, and as identical as possible in appearance.

Randomization data will be kept strictly confidential by PPD, accessible only to authorized persons, until the time of unblinding. After the study is completed, the data file verified, and protocol violations determined, drug codes will be broken and made available for data analysis.

5.2 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be electronic. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the study team prior to breaking the blind unless the delay would endanger the subject's health. When the blinding code is broken, the reason must be fully documented and entered in the case report form (CRF).

Any AE or serious AE (SAE) associated with breaking the blind must be recorded and reported as specified in this protocol. The study site is required to inform the IRB/EC if the blind is broken.

5.3 Subject Compliance

All doses will be applied by a trained nurse, either at investigational site, at subject's home, or at a site convenient for the subject following an established method to ensure consistent application.

Additionally, the tubes of study treatment will be weighed prior to dispensing to subjects and upon return to study site.

5.4 Investigational Product Supplies

5.4.1 Dosage Form and Packaging

Table 5-1 Test Product Information

	Active Treatment	Placebo Control
Product Name	Diclofenac diethylamine 2.32% gel	Placebo gel, 0% Diclofenac gel
Pack Type	Kit of 2 x 100 g tubes	Kit of 2 x 100 g tubes
Dispensing Details	1 per subject at visit 2	1 per subject at visit 2
Product Formulation Code	CCI [redacted]	CCI [redacted]
Dose	Gel – 4 g on 400 cm^2	Gel – 4 g on 400 cm^2
Route of Administration	Topical	Topical
Usage Instructions	Twice a day (b.i.d)	Twice a day (b.i.d)
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned

Table 5-2 Rescue Medication Information

	Rescue Medication
Product Name	500 mg paracetamol tablets
Pack Type	Pack of tablets
Dispensing Details	Dispense at Visit 1
Product Formulation Code	Commercial product
Dose	1-2 tablets with water
Route of Administration	Oral

Usage Instructions	As required up to 4 g/day. A maximum of 2 tablets per dosing occasion.
Return Requirements	All used/unused samples to be returned

Table 5-3 Sundry Items to be supplied

Item Name	Supplied By	Pack Type	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Urine drug test	GSK	Each	To be used by site staff at visit 1	Dispose at site	Return
Urine pregnancy test	GSK	Twin test pack	To be used by site staff at visit 1 and 2	Dispose at site	Return
Dosing Card	GSK	Each	Included in treatment kit	Return	Return
Derm pen (skin marker pen)	GSK	Each	To be used by study staff as required	Dispose at site	Return
Stencil	GSK	Each	To be used by study staff as required	Dispose at site	Return

For return of items please refer to the supplied instructions which will be provided by GSKCH during the course of the study in time for study close out.

5.4.2 Preparation and Dispensing

Study treatment will be dispensed to the subject by qualified site personnel after randomization at Visit 2. Each participant will be dispensed blinded study treatment, labeled with the assigned kit number, and rescue medication.

The tubes of study treatment will be weighed prior to dispensing to subjects and upon return to the study site.

5.5 Administration

The study treatment will be applied twice a day for seven days. The first and last dose of study treatment will be applied by a trained study nurse at the study site. The doses in between first and last dose will be applied by a trained study nurse at the subject's home or at a place convenient for the subject.

A 4 gram dose, measured with a dosing card, will be applied over a 400 cm^2 surface of the knee identified for treatment (target knee). The area will be identified and recorded using a derm pen and a stencil before the first dose to permit consistent redosing at the same site. The nursing staff will undergo training to ensure dosing can be done in a consistent manner.

The study nurse, wearing gloves, will spread a dose of study treatment, measured using a dosing card, on the subject's target knee. The study treatment should be rubbed gently into the skin for about 1 minute over a region of approximately 400 cm^2 per knee (i.e., about the surface of the two palms of the hands). Doses should be applied at intervals as close as possible to every 12 hours.

The treated area must not be covered within the first 10 minutes or washed, bathed, or showered within the first three (3) hours after the application.

The application site should not be occluded. The use of heat or heat pad on the target knee is not allowed.

5.5.1 Medication Errors

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

- the wrong product,
- by the wrong subject,
- at the wrong time,
- on the wrong knee,
- or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not a medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on the appropriate CRF page.

5.6 Investigational Product Storage

The investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products including any comparator, marketed products and rescue medication are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and 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 investigational 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 as detailed on the Clinical Supplies Checklist form should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the proper storage requirements for take-home investigational products.

5.7 Investigational Product Accountability

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

Study treatments 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 treatments should be stored according to the instructions specified on the treatment labels. Clinical supplies are to be dispensed only in accordance with the protocol.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs including rescue medication will be accounted for using a drug accountability form/record.

All unused products must be returned to the study site at Visit 3. The monitoring plan will describe the process for investigational product accountability.

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

5.7.1 Destruction of Investigational Product Supplies

All investigational study treatments, rescue medication and sundry items as detailed in Table 5-1, Table 5-2 and Table 5-3 shipped for this clinical trial will be returned to the Sponsor at the

termination of the study. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH will inventory all used and unused investigational study treatment. The study treatment inventory record for returned study treatment will then be completed. All investigational product for this clinical study (empty containers), as well as all unused study product will be returned to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

5.8 Concomitant Treatment(s)

As a general rule, no concomitant medications will be permitted during the study, especially those medications prohibited by the exclusion criteria. Special attention should be given to the prohibited use of systemic or topical NSAIDs from the time of Screening (Visit 1) up to completion of surgery – as these are the basis for subject exclusion.

Subjects will receive paracetamol as rescue medication as described in Section 5.9. Should the need arise for additional pain relief, the investigators will be allowed to prescribe codeine or tramadol.

Medications to treat adverse events prior to the surgery may only be prescribed after consultation with the Sponsor (with the exception of paracetamol, and if needed codeine or tramadol), unless there is an emergency situation that does not allow discussion.

All concomitant treatments taken during the study must be recorded with indication, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit and by the study nurse at each home/convenient place visit.

Treatments taken within 90 days before the screening visit (visit 1) and up to the last study visit (Visit 4) will be documented in the CRF. Treatments taken after starting washout or whose dose changes after randomization will be documented as concomitant medication.

Use of hormonal contraception will be allowed during the study; however, subjects must have been stabilized on this medication for at least 3 months prior to screening.

Subjects will be allowed to remain on any maintenance medication not excluded by the exclusion criteria, provided they have been stabilized on this medication for at least 3 months prior to screening.

5.9 Rescue Medication

The subjects will be provided rescue medication (paracetamol, 500 mg tablets) at the screening visit (Visit 1). Subjects are instructed to take only the rescue medication provided for pain in the knee or any other pain (e.g., headache) or fever (e.g., due to common cold) they might experience during the study. One or two tablets may be taken, repeated after at least 4 hours up to four times a day, if needed, up to a maximum of 4 g per day.

Paracetamol has been selected as rescue therapy because it provides analgesia and is used for OA pain (UK NICE Guidelines). It will not alter the disposition of diclofenac (by altering plasma protein binding or tissue blood flow) and it is not expected to significantly affect COX-2

inhibition. Paracetamol is > 100 times less potent as a COX-2 antagonist and is expected to have minimal effect on the biomarkers under consideration (FitzGerald 2001).

Care must be taken to ensure that the subject understands that any other use of paracetamol or paracetamol containing combination treatments must be avoided to ensure they do not exceed the maximum daily dose.

Subjects will be questioned about use of rescue medication at each clinic visit, and by the study nurse at each home/convenient place visit. All rescue medication used during the study will be recorded into the CRF.

6 STUDY PROCEDURES

6.1 Screening (Visit 1) From Day -10 up to Day -7

Subjects will be screened 7-10 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject.

The following procedures will be completed and recorded in source documents:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Collect demography (age, gender).
- Collect height and weight.
- Obtain medical history, including history of illegal drug and alcohol use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 3 months prior to Visit 1.
- Conduct full physical examination and collect vital signs (blood pressure (BP), pulse rate (PR), RR, temperature).
- Collect standard 12-lead electrocardiogram (ECG).
- Instruct subject in ceasing all NSAID treatment and in use of rescue medication
- Instruct subject on study requirements
- Assess eligibility.
- Dispense rescue medication
- Following at least a 4-hour fast, collect blood and urine specimens for the following:
  - Safety laboratory tests;
  - Urine drug screening;
  - Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months;
  - Urine β-hCG for all females of childbearing potential.
- Review any AEs

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.2 Study Period

6.2.1 Baseline (Visit 2) Day 1

The baseline visit will take place in the morning, to allow for twice a day dosing of study medication on Day 1. The following procedures will be completed and results recorded in source documents.

Prior to Randomization on Day 1:

- Review Inclusion and Exclusion criteria
- Review safety laboratory test results from Screening Visit. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1.
- Review concomitant medications
- Review any AEs
- Collect urine pregnancy test for females of childbearing potential.
- Confirm proper contraception is being used.
- Conduct physical examination and collect vital signs (BP, PR, RR, temperature) .
- Assess eligibility and randomize eligible subjects

Following Randomization on Day 1:

- Collect a 5 ml PK blood draw within one 1 hour prior to first dosing
- Dispense study treatment
- Apply first dose of study treatment to the target knee (only the knee scheduled to undergo arthroplasty) at study site.
- Organization of nursing schedule for home visits

6.2.2 Between Visit 2/Day 1 and Visit 3/Day 7:

- A study nurse will visit the subject's home/convenient place to apply study treatment to the target knee twice a day, between Visit 2 and Visit 3. The last dose applied by the study nurse at the subject's home will be on the morning of Day 7.
- The study nurse will record, in an agreed upon source data collection tool, dosing of study treatment at each visit to the subject's home.
- The study nurse will record, in an agreed upon source data collection tool, use of rescue medication, concomitant treatments and adverse events reported by the subject.

6.2.3 Pre-Surgery Day 7 and Surgery Day 8 (Visit 3)

The subject will be admitted to the study site in the afternoon of Day 7 and remain at the study site until discharge post-surgery. The surgery will take place in the morning of Day 8, 12 hours (window -1/+3 hrs) after last dose of study treatment.

The surgery may be delayed by up to 7 days, in which case the study treatment will continue to be applied twice daily up to 14 days. If the surgery is delayed by more than 7 days, the subject should be withdrawn from the study. Subject Withdrawal/Early Termination assessments will be conducted (See Section 6.4 Subject Withdrawal). No further PK blood samples will be collected and the rescheduled surgery will not be part of the study.

On Day 7 (pre-surgery), the following procedures will be completed and results recorded in source documents:

- Collect all returned study treatment
- Collect all returned rescue medication
- Review concomitant medications
- Review any AEs (continuing up to surgery)
- Collect a blood sample for pharmacokinetic analysis within 1 hour prior to last dosing.
- Dose subject with final dose of study treatment (12 hours (window -1/+3 hrs) prior to surgery)

After dosing, (ie. Between final dosing with study treatment and prior to surgery) the following procedures will be completed:

- Conduct physical examination and collect vital signs (BP, PR, RR, temperature)
- Collect standard 12-lead ECG measurements
- Following at least a 4 hour fast, collect blood and urine specimens for safety laboratory tests
- Collect one blood sample for diclofenac levels —at least 3 hours after dosing and more than 3 hours before surgery
- The subject will be prepared for surgery according to the procedures of the surgical center; if shaving of the knee area is required, this should occur as close as possible to the surgery but in any event no less than 3 hours after dosing

During Surgery

- The surgery will be conducted according to the surgical procedures of the surgical center
- One final blood sample for PK analysis will be collected (between anaesthesia and completion of surgery)
- Four (4) aliquots of 2.5-3 mL of synovial fluid will be collected as described in the Laboratory Study Manual

- Two (2) synovial tissue samples of approximately 2 to 3 cm^3 each will be collected as described in the Laboratory Study Manual

6.3 Follow-up Visit (Visit 4) Day 8-10

The follow up Visit will take place after the surgery prior to discharge of the subject from the surgical center.

At this visit the following procedure will be conducted and results recorded in the source documents.

- Conduct physical examination and collect vital signs.
- Standard 12-lead ECG.
- Following at least a 4-hour fast, collect blood and urine specimens for safety laboratory tests
- Review concomitant medications
- Record any AEs
- The subject will be discharged from the study

6.4 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

- Surgery delayed by more than 7 days
- Development of a skin rash after study gel application
- Protocol violation that may impact the outcome of the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Pregnancy
- Death

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, clinical site staff must send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the source document. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject returns all unused investigational products and rescue medication, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

In the case of subject withdrawal/early termination, the following assessments should be performed and results recorded in the source documents:

- Physical examination and vital signs;
- 12-lead ECG measurement;
- Blood and urine specimens for safety laboratory and pregnancy tests (if applicable);

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 also 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.

7 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 perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test 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 study team must be informed of these incidents in a timely manner.

7.1 Safety

The following safety assessments will be performed at times defined in the Study Procedures section of this protocol.

7.1.1 Laboratory Tests

Planned laboratory tests are displayed in table 7.1. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyser used by the clinical laboratory; or as derived from calculated values. These additional tests would not require

additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Blood and urine Human Biological Samples (HBS) will be collected for safety laboratory tests. The volume of individual blood samples collected will be up to 15 mL and the volume of individual urine samples collected will be up to 50 mL. All samples will be assigned unique tracking identifiers. Samples (blood and urine) will be processed, labelled and transferred to the analytical laboratory of the study site the same day as collection. The samples will be processed and stored per the local laboratory standard procedures, and destroyed within 7 days of testing. All samples will be tracked from collection to destruction on a HBS Tracking Log.

Table 7-1 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count MPV WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose (fasting) Calcium Magnesium Sodium Potassium Chloride Total CO2(Bicarbonate) AST, ALT Direct Bilirubin Indirect Bilirubin Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine Bilirubin Specific gravity Microscopy[a]	Urine drug screen[b] Serum FSH[c]
	Additional tests[e]		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

Definitions: RBC= Red blood cell; MCV= Mean corpuscular volume; MCH= Mean corpuscular hemoglobin; MCHC= Mean corpuscular hemoglobin concentration; MPV= Mean platelet volume; WBC= White blood cells; BUN=Blood urea nitrogen; HIV= Human immunodeficiency virus; AST=

transaminase; ALT= alanine transaminase; PT/INR= prothrombin time/ international normalized ratio; GGT= Gamma-glutamyl transpeptidase.

[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

[b] Minimum requirement for drug testing includes: cocaine, THC, opiates/opiods, benzodiazepines and amphetamines

[c] FSH done at Screening only in females who have been amenorrheic for 1 year.

7.1.2 Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at Screening (Visit 1) and Baseline (Visit 2). Results will be obtained prior to randomization.

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected), and at a subject's early withdrawal from the study. Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.1.3 Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, vascular and neurological systems.

Clinically significant abnormalities that are present prior to signing ICF must be included in the Relevant Medical History/Current Medical Conditions CRF page. Any untoward findings identified on physical exams conducted after signing ICF will be captured as an adverse event, if those findings meet the definition of an adverse event.

7.1.4 Height and Weight

Height in centimeters (cm) and body weight in kilograms (kg) to the nearest 0.1 kilogram will be measured at Screening (Visit 1).

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.5 Blood Pressure and Pulse Rate

Blood pressure (taken whilst sitting) and pulse rate will be measured at times specified in the Study Procedures section of this protocol. Values will be recorded in the CRF. Additional

collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary at the discretion of the investigator, to ensure appropriate collection of safety data.

Blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.6 Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

7.1.7 Temperature

Temperature will be measured orally.

No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.1.8 Electrocardiogram

A standard 12-lead ECG is performed at the screening visit (Visit 1), the pre-surgery visit (Visit 3) and the follow up visit (Visit 4). Interpretation of the tracing must be made by a qualified physician and documented in the CRF. Each ECG tracing should be labeled with the study number, subject number and date, and be kept in the source documents at the study site. Only clinically significant abnormalities should be reported in the CRF.

Clinically significant abnormalities that are present prior to signing ICF must be included in the Relevant Medical History/Current Medical Conditions CRF page. Clinically significant findings must be discussed with the Sponsor prior to enrolling the subject in the study. Clinically significant abnormalities found after signing ICF which meet the definition of an AE must be recorded in the Adverse Event CRF page.

7.2 Pharmacokinetics (PK)

7.2.1 Plasma for Analysis of Diclofenac

During all study periods, blood samples of 5 mL to provide a minimum of 2 mL plasma for pharmacokinetic analysis will be collected into appropriately labeled plastic tubes containing potassium-ethylenediaminetetraacetic acid (K2-EDTA) at times specified in the Study Procedures section of the protocol.

Four samples are planned for collection:

- One blood sample at baseline within one hour prior to administration of study treatment (Visit 2/Day 1),
- One blood sample within one hour prior to last dose of study treatment (Visit 3/Day 7),
- One blood sample between last dose of study treatment and commencement of surgery (not to occur within 3 hours of last dosing or less than 3 hours before surgery),
- One blood sample during surgery on Day 8 (between anaesthesia and completion of surgery),

And will be collected within the specified time windows and sample collection time should be noted on the source document and the CRF.

The collection, processing, storage and shipping of the blood samples will be described in a laboratory manual provided by the bioanalytical laboratory (PAREXEL Bloemfontein, South Africa). Briefly, blood samples will be taken into supplied tubes which will then be centrifuged to isolate plasma. The plasma will be transferred into provided storage tubes which will be frozen until shipping to the bioanalytical laboratory.

Samples will be analysed for diclofenac levels using a validated bioanalytical method in compliance with the applicable standard operating procedures of the bioanalytical laboratory.

The PK samples must be processed, stored and shipped as indicated in the laboratory manual to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

The samples will be retained for 6 months after approval of the Clinical Study Report and the sponsor will confirm authorization of destruction.

7.2.2 Synovial Tissue and Synovial Fluid

During surgery, synovial tissue and synovial fluid will be collected into appropriately specimen containers following preparation detailed in the laboratory manual.

The samples planned for collection are:

- Two (2) synovial tissue samples of approximately 2 to 3 cm^3 each
- Four (4) aliquots of 2.5-3 mL of synovial fluid

The tissue and fluid samples will be collected within the TKR surgery with their specific collection time noted.

The collection, processing, storage and shipping of the tissue and fluid samples will be described in a laboratory manual provided by the bioanalytical laboratory. Briefly, samples will be transferred into appropriate specimen containers, will have any additional treatments (as defined by the laboratory manual) and be frozen immediately after surgery prior to shipping to the bioanalytical laboratory.

The samples will be analysed for diclofenac levels using a validated bioanalytical method in compliance with the applicable standard operating procedures of the bioanalytical laboratory.

All samples must be processed, stored and shipped as indicated in the laboratory manual to maintain sample integrity. Any deviations from the steps described in the laboratory manual, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

All samples will be retained for 6 months after approval of the Clinical Study Report and the sponsor will confirm authorization of destruction.

7.2.3 Shipment of all Samples

The shipment address for all samples is:

FARMOVS PAREXEL (Pty) Ltd

Kampuslaan Suid

Campus of the University of the Free State (Nelson Mandela Drive)

Bloemfontein, 9301

South Africa

7.3 Pharmacodynamics

The synovial tissue and fluid samples will also be analysed for biomarkers including IL-6, PGE_2 and TNFα. These samples will be analysed under the responsibility of Parexel South Africa and treated and stored as indicated in the laboratory manual.

7.3.1 Pharmacodynamic Markers

The synovial tissue and fluid samples will be analysed for biomarker levels using a validated exploratory bioanalytical method in compliance with the applicable standard operating procedures of the bioanalytical laboratory. The biomarkers evaluated include:

- PGE_2 – a protein produced via the enzyme COX-2. Inhibition of COX-2 reduces levels of PGE_2.
- IL-6, TNFα – proinflammatory cytokines responsible for inflammation and reduced by anti-inflammatory treatments

As part of understanding the pharmacodynamics of the study drug, samples may be used for evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.4 Blood Volume

The total blood sampling volume for each subject in this study is approximately 65 mL. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at the discretion of the investigator or GSK CH.

Table 7-2 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs	15	1	1	1	45
PK	5	0	4	0	20
TOTAL					65

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

8 ADVERSE EVENT AND OTHER EVENTS OF SPECIAL INTEREST REPORTING

8.1 Definitions of Adverse Events and Serious Adverse Events

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of an investigational or washout product or medical device, whether or not considered related to the investigational or washout product or medical device.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 signing ICF 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 treatment 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.

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 and the scheduled surgical intervention, 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, including the scheduled surgical intervention, unless judged by the investigator to be 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.

8.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization 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 participant 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 hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant 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 hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization 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, diarrhea, influenza, and accidental trauma (eg, 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 hospitalization but may jeopardize the participant 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 hospitalization, or development of drug dependency or drug abuse.

8.2 Reporting Period

8.2.1 Adverse Event

AEs (serious and nonserious) will be collected from the time the subject has signed informed consent and until 28 days following last administration of the investigational product.

8.2.2 Serious Adverse Event

SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product and until 28 days following last administration of the investigational product.

SAEs assessed as **not related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or not related to a GSK concomitant medication will be recorded from the signing of the ICF and until 28 days following last administration of the investigational product.

8.3 Reporting Procedures

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

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

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

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, 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/SAE in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

AEs elicited by the investigator in a standard manner at the study visits and by the study nurse at the subject's home should also be recorded in the AE section of the CRF. Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.1 Adverse Event

All AEs will be reported on the AE page(s) of the CRF 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 CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AE should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

8.3.2 Serious Adverse Event

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH 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 on study product
- Outcome if known

The SAE form, completed as fully as possible, must be sent to PPD **immediately and under no circumstance should this exceed 24 hours** of awareness.

SAE Contact Information:
PPD, Medical Affairs/Pharmacovigilance
Granta Park, Great Abington
Cambridge, CB21 6GQ, United Kingdom
PPD Pharmacovigilance Hotline: PPD
PPD Pharmacovigilance Fax Line: PPD
Email: PPD

PPD will then email the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK PPD, with copy to the appropriate GSK CH Study Manager as soon as possible, **but not later than 1 business day** after study site personnel learn of the event. The GSK CH Study Manager will be responsible for forwarding the SAE form to other GSK CH personnel as appropriate.

8.3.3 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4 Evaluating Adverse Events and Serious Adverse Events

8.4.1 Severity Assessment

The investigator or designee will make an assessment of severity for each AE and SAE 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 will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both 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.

8.4.2 Causality Assessment

The causality assessment is one of the criteria used when determining regulatory reporting requirements. 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 CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if 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.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always makes an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** 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.

8.5 Withdrawal Due to an Adverse Event and Serious Adverse Events

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

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

8.6 Pregnancy

8.6.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported following administration of any investigational product and until 21 days after the last dose.

8.6.2 Action to be Taken if Pregnancy Occurs

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 PPD 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 PPD. 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 (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be and should be recorded as an SAE.

Any female participant who becomes pregnant while participating will discontinue study treatment and be withdrawn from the study.

Like with SAE and Incident Forms, PPD will then email the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD) with copy to the appropriate GSK CH Study Manager.

8.7 Follow-up of Adverse Events and Serious Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

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 GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

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

Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSK by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD). The GSK CH Study Manager or designee will be responsible for

forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK).

The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

9 DATA MANAGEMENT

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

For this study subject data will be entered into an electronic CRF, using a validated data system.

9.1 Source Documents/ Data

The source documents (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Section 6. The CRF can be used as a source document at the discretion of data management.

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

9.2 Case Report Form

A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with PPD applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data e.g., removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

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

GSK CH will obtain and retain all CRFs and associated study data at the completion of the study.

9.3 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.

Any corrections to the entries made to the source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

9.3.1 Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, 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 (Adverse Events and Drugs) appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and 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 CRFs, to raise manual queries as needed for site clarification or correction.

9.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

10 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1 Sample Size Determination

A formal estimation of sample size was not carried out. The sample size selected (approximately 30 subjects on active, 15 subjects on placebo control) for the present study is in general agreement with similar studies (Benito 2005, Gallelli 2013, Gallelli 2012, Alvarez-Soria 2006, Fowler 1983, Efe 2014) and is deemed adequate to provide information on diclofenac concentration(s) in treated knee synovial tissue and synovial fluid.

Approximately 50 subjects will be randomized to account for 10% dropout and ensure evaluable data for 45 subjects who underwent the surgery.

10.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical reporting analysis plan (RAP), which will be written following finalization of the protocol and prior to study unblinding.

10.2.1 Definition of Analysis Populations

The safety population will include all subjects who are randomized and have received at least one dose of investigational product.

The analysable population will consist of all subjects included in the safety population, who completed the surgery and have evaluable synovial tissue or synovial fluid sample.

The Per-Protocol (PP) population includes all subjects from the analysable population who do not have any major protocol deviations that could confound the interpretation of analyses conducted on the analysable population. Protocol deviations that would exclude subjects from the PP population are defined in Section 10.2.2.

The breakdown of subjects into the analysis sets will be presented.

10.2.2 Exclusion of Data from Analysis

All evaluable data will be included in the analysis.

Protocol deviations that would exclude subjects from the PP population may include (but are not limited to) the following:

- Major deviations in synovial tissue and synovial fluid sampling
- Subjects with poor compliance with study treatment
- Subjects taking prohibited medication or treatment during the study which is felt to affect the assessment of synovial tissue and synovial fluid samples.

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting and documented in the RAP prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

10.2.3 Demographic and Baseline Characteristics

Demographic and other baseline data will be presented using descriptive statistics and will be listed.

Categorical variables will be summarized by the number and percentage of subjects with each relevant characteristic. Continuous variables will be summarized by calculating the mean, standard deviation, median, minimum and maximum.

10.2.4 Study Drug/Product Compliance and Use of Other Therapies

10.2.4.1 Study Drug/Product Compliance

Compliance with study drug will be summarised in the analysable population as the number of subjects with a minimum of 12 applications before surgery.

10.2.4.2 Prior and Concomitant Medications

Other medications will be listed in the safety population. Concomitant medications will be summarized by preferred term, and the number and percentage of subjects who took any concomitant medication, will be presented.

10.2.4.3 Other Therapy/Rescue Medication (if applicable)

The use of rescue medication (number of subjects that used rescue medication, number of days on rescue medication and total dose of paracetamol taken) will be presented by treatment group for the analysable population.

10.2.5 Primary Analysis(es)

Evaluation Criteria

The success criterion of this study is that diclofenac can be detected within the treated knee synovial tissue or synovial fluid after 7 days treatment.

Analysis

The primary endpoints are diclofenac concentrations in treated knee synovial tissue and synovial fluid at 12 hours after last administration.

Synovial tissue and synovial fluid diclofenac concentrations will be summarized descriptively by treatment group in both the arithmetic and the logarithmic scale. The tables will present the proportion of subjects with values above the limit of quantification (LOQ) with its two-sided 95% confidence interval. The mean, SD, min, P10, Q1, median, Q3, P90, max will be calculated after replacing values below the LOQ by LOQ/2. The geometric mean will also be calculated with a two-sided 95% confidence interval assuming data on the logarithmic scale are normally distributed. Boxplots by treatment group will be produced on the original data.

The analysis will be performed on the analysable population.

10.2.6 Secondary Analysis(es)

Evaluation Criteria

The secondary objective is to evaluate the relative exposure of diclofenac in the knee joint vs. plasma.

Analysis

The secondary endpoints are

- Ratio between diclofenac concentration in treated knee synovial tissue and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application)
- Ratio between diclofenac concentration in treated knee synovial fluid and diclofenac plasma concentration (sample taken during surgery) after 7 days topical application of study treatment to the knee (12 hours after last application)

Following the same approach as for the primary endpoints, the ratios between diclofenac concentration in synovial tissue / fluid and diclofenac plasma concentration (last sample taken during surgery) will be summarized descriptively by treatment group in both the arithmetic and the logarithmic scale. Geometric means will be calculated with two-sided 95% confidence intervals. Boxplots by treatment group will be produced.

The analysis will be performed on the analysable population.

10.2.7 Safety Analysis(es)

Safety variables will be summarized on the safety population.

Exposure to study drug (number of applications, total weight of gel used) will be summarized by treatment group.

Treatment Emergent adverse events (TEAE, i.e. AEs that start or worsen after first study treatment administration) will be summarized by presenting, for each treatment group, the number and percentage of subjects having any TEAE, any TEAE in each MedDRA primary System Organ Class (SOC) and having each individual TEAE (using MedDRA preferred term). This will be done separately for all TEAEs and for TEAEs that are suspected to be drug-related. All TEAEs will also be tabulated in corresponding fashion by severity. Any other information collected (e.g. action taken, duration, outcome, seriousness) will be listed as appropriate.

All adverse events (prior to treatment and treatment emergent) will be listed.

Chemistry and hematology results at screening, Visit 3 and at Visit 4 will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group. Shift tables (between baseline and Visit 3, between Visit 3 and Visit 4) will also be presented. Laboratory normal ranges and all laboratory test results will be listed.

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate) recorded at Visit 3 and changes in vital signs from Visit 2 (baseline) to Visit 3 will be summarized by the mean,

standard deviation, median, minimum and maximum values in each treatment group. Vital signs at each assessment will also be listed.

ECG results at Visit 3 and Visit 4 will be summarised.

10.2.8 Other Analysis(es)

Evaluation Criteria

The success criteria for exploratory objectives are that

- diclofenac reduces PGE_2 levels in treated knee synovial tissue or synovial fluid after 7 days topical administration to the knee compared to placebo gel
- diclofenac reduces levels of inflammatory cytokines i.e. TNF_α and IL-6 associated with OA in treated knee synovial tissue and synovial fluid after 7 days topical administration to the knee compared to placebo gel

Analysis

The exploratory endpoints are

- PGE_2 levels in treated knee synovial tissue and synovial fluid after 7 days topical administration to the knee (12 hours after last application)
- IL-6 and TNF levels in treated knee synovial tissue and synovial fluid after 7 days topical administration to the knee (12 hours after last application)

PGE_2 and inflammatory cytokines levels will be summarized descriptively in both the arithmetic and the logarithmic scale.

For each endpoint, the success criterion will be addressed by a two-sided test for superiority at level alpha=0.05 in an exploratory manner. Log-transformed mean levels will be compared between treatment groups using an analysis of variance including treatment as a fixed effect. The two-sided 95% confidence interval for the ratio of geometric means on the original scale will be derived by back-transforming the confidence interval for the difference between treatment groups on the log-transformed scale obtained from the analysis.

The analysis will be performed on the analysable population.

Diclofenac plasma concentrations will also be summarized on the analysable population by calculating the mean, standard deviation, median, minimum and maximum for the following timepoints: Visit 2 (baseline), Visit 3 (pre-dose), Visit 3 (sample taken between last application and surgery) Visit 3 (last sample taken during surgery).

10.2.9 Handling of Dropouts and Missing Data

Missing data will not be imputed. All evaluable parameters after 7 days from subjects in the analysable population will be used in the analysis of primary, secondary and exploratory endpoints. Values that are below the limit of quantification (BLOQ) will be replaced by LOQ/2.

10.2.10 Interim Analysis

No interim analysis is planned for this study.

11 STUDY GOVERNANCE CONSIDERATIONS

11.1 Quality Control

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) 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 GSK requirements.

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

GSK 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 GSK CH. 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 in the course of these monitoring visits are resolved.

11.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK 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(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the

regulatory authority, the investigator will provide GSK CH 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.

11.3 Regulatory and Ethical Considerations

11.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent 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 GSK CH 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 GSK CH in writing immediately after the implementation.

11.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, 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), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

11.3.3 Subject Information and Consent

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 GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH 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, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

11.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening 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.

GSK CH 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.

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

Within GSK CH 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 GSK CH- 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, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH 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 or of ICH GCP that the investigator becomes aware of.

11.4 Posting of Information on Publicly Available Clinical Trial Registers

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

11.5 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 GSK site or other mutually-agreeable location.

GSK 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 GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11.6 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 GSK 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 of 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 CRFs or other documents submitted to GSK CH, 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 GSK CH, 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 for 25 years from the issue of the final Clinical Study Report (CSR)/ 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, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK 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.

11.7 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 investigational product safety problems, or at the discretion of GSK CH. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If a study is prematurely terminated, GSK CH 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 GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH 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/favorable opinion of a trial, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

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

11.8 Definition of Study End/ End of Study

The study end date will be the same date as Last Subject Last Visit.

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13 APPENDIX

13.1 ABBREVIATION

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

Table 13-1 Abbreviation

Abbreviation	Term
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
b.i.d.	twice daily
BLOQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CO_2	carbon dioxide (bicarbonate)
COX-2	cyclo-oxygenase 2
CRF	case report form
DDEA	Diclofenac diethylamine
EC	ethics committee
ECG	electrocardiogram
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device

Abbreviation	Term
K2-EDTA	potassium-ethylenediaminetetraacetic acid
LOQ	Limit Of Quantification
max	maximum
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
min	minimum
N/A	not applicable
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OTC	over-the-counter
P10	10^{th} percentile
P90	90^{th} percentile
PD	pharmacodynamics
PG	prostaglandin
PGE_2	prostaglandin E2
PI	principal investigator
PK	pharmacokinetics
PP	Per-Protocol
PR	pulse rate
PT	prothrombin time
Q1	First quartile
Q3	Third quartile
RAP	reporting analysis plan
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SOC	System Organ Class
SRSD	single reference study document
SS	safety statement
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal half-life
TEAE	Treatment Emergent adverse event
TKR	total knee replacement
US	United States

Abbreviation	Term
WBC	white blood cell