GlaxoSmithKline
Consumer Healthcare

CLINICAL PROTOCOL

A randomized, double blind, multi center, active-controlled, 2 treatment arm, parallel group non inferiority study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice daily versus diclofenac diethylamine 1.16% gel applied four times daily for one week in subjects with acute ankle sprain

Protocol Number:	211206
Compound/Product Name:	Diclofenac Diethylamine 2.32%
United States (US) Investigational New Drug (IND) Number:	NA
European Clinical Trials Database (EudraCT) Number:	NA
Other Regulatory Agency Identified Number:	National Medical Products Administration (NMPA) Number_2016L09875
Phase:	Phase III

Sponsor Information

Sponsor Name & Legal Registered Address	**GSK Consumer Healthcare Schweiz AG** 6343 Risch Switzerland
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	1.0	Refer to Summary of Changes document

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

Principal Investigator Protocol Agreement Page

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

Investigator Name:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/Agreement:	DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

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 diclofenac diethylamine (DDEA) 1.16% gel (Voltarol Emulgel in the UK, and generic name of DDEA Emulgel was registered in China) 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).

As part of the global expansion for the product, China has been identified as a desirable market for registration of DDEA 2.32% gel. The identified registration pathway in China for the DDEA 2.32% gel is variation specifying addition of a new strength to the already registered DDEA 1.16% gel (License Number H20181225/H20181226, firstly issued on March 12, 2013), with the same indications as currently registered for DDEA 1.16% gel, i.e. for the relief of mild to moderate pain in muscles, soft tissues, and joints, e.g. muscles or soft tissue pains caused by sprain, pulling injury, contusions, strain, waist-back injury and various arthralgia etc, and for symptomatic treatment of osteoarthritis.

In support of the proposed registration, the National Medical Products Administration (NMPA) approved a clinical trial application (CTA) on November 06, 2016 (CTA No. 2016L09875). The approved CTA stipulated that a non-inferiority study assessing the efficacy and safety of the DDEA 2.32% versus that of the registered DDEA 1.16% should be conducted in a local population.

To this effect, GSKCH intends to conduct a randomized, double blind, multi-center, active controlled, parallel group, non-inferiority study to evaluate the efficacy and safety of DDEA 2.32% gel applied twice daily versus DDEA 1.16% gel applied four times daily in subjects with ankle sprain in China.

Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To demonstrate non-inferiority between DDEA 2.32% and DDEA 1.16% with regard to pain relief after acute ankle sprain	Change from baseline in pain on movement (POM) on Day 5 of treatment as assessed by a 100 mm VAS scale
Secondary	
To assess safety of DDEA 1.16% and DDEA 2.32% gels after 1 week of use	Number, incidence, and severity of adverse events following dosing with study medication
To assess efficacy of treatments for pain relief as measured by POM on Days 3 and 8	Change from baseline of POM on VAS on Day 3 and Day 8 of treatment assessed by 100 mm VAS scale
To assess efficacy of treatments for inflammation of the affected ankle as measured by pressure algometry on Days 3, 5, and 8	Change from baseline in tenderness as measured by pressure algometry on Days 3,5, and 8
To assess efficacy of treatments for inflammation of the affected ankle as measured by pressure algometry on Days 3, 5, and 8	Difference between measurement in affected ankle and contralateral ankle on Days 3,5,and 8
To assess efficacy of treatments for ankle joint function as measured on the Karlsson Scoring Scale	Change from baseline in Ankle Joint Function (Karlsson Scoring Scale) on Days 3,5, and 8

To assess efficacy of treatments for swelling of affected ankle as measured by Figure of Eight Method	Change from baseline in circumference of affected ankle as measured by Figure of Eight method on Days 3,5, and 8
To assess efficacy of treatments for swelling of affected ankle as measured by Figure of Eight method	Difference between circumference of affected ankle to unaffected ankle by Figure of Eight method on Days 3, 5, and 8
To assess efficacy of treatments for effect on pain intensity as measured by Sum of Pain Intensity Difference (SPID)	SPID from 0 – 24 hours post first dose (Day 1) and from 96 – 120 hours post first dose (Day 5)
To assess effect of treatments for effect on pain relief as measured by Total Pain Relief (TOTPAR)	TOTPAR from 0 – 24 hours post first dose (Day 1) and from 96 – 120 hours post first dose (Day 5)
To assess the use of rescue medication among subjects	Number of tablets used to treat ankle pain and overall
To assess the use of rescue medication among subjects	Number of days on which rescue medication was used to treat ankle pain and overall

Study Design

This is a Phase III, randomized, double blind, multi-center, active controlled, 2 treatment arm, parallel group, non-inferiority study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice daily versus diclofenac diethylamine 1.16% gel applied four times daily for 1 week in subjects with acute ankle sprain.

To qualify, subjects must experience an acute Grade I -II sprain of the ankle within the past 24 hours. Subjects should be randomized as soon as possible after the injury.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the following two treatment arms:

Treatment Schedule

Treatment Arms	Morning (Upon Rising)	Noon	Late Afternoon (evening)	Late Evening (bed time)
DDEA 2.32% four times daily	DDEA 2.32% gel	Placebo gel	DDEA 2.32% gel	Placebo gel
DDEA 1.16% four times daily	DDEA 1.16% gel	DDEA 1.16% gel	DDEA 1.16% gel	DDEA 1.16% gel

Approximately 300 subjects (150 in each group) with acute ankle sprain are to be randomized. All subjects will receive four (4) tubes of study drug, for treatment in morning, noon, late afternoon, and late evening, respectively. The very first dose of study drug will be applied at the study center. The subjects will be instructed to apply the gel topically with the finger tips (for approximately 1 minute) in the morning, at noon, late afternoon, and late evening for 7 days. Each tube will be labeled for use at one of these 4 times.

After the randomization visit (Visit 1/baseline visit), subjects will return to the study site for post baseline visits, namely Visit 2, Visit 3, and Visit 4 to complete efficacy and safety assessments. Baseline safety laboratory test blood samples will be taken. End of study safety laboratory tests will also be taken at Visit 4, or in case of early termination. In addition, subjects (ex-clinic) will assess pain intensity and pain relief at frequent intervals on Day 1 and then at

each study drug application throughout the rest of the study. The schedule of visits is described below.

Study center visits per subject:

Screening / Randomization visit [Visit 1]	Day 1 (0 h)
1st interim visit [Visit 2]	Day 3 (48 ± 4 h after initiating treatment)
2nd interim visit [Visit 3]	Day 5 (primary endpoint measurement) (96 ± 4 h after initiating treatment)
Final visit [Visit 4]	Day 8 ± 1 d (7 ± 1 days after initiating treatment)

Study Products

The following products will be administered in this study:

	Active Treatment[a]	Active Comparator[b]	Placebo Product for Blinding of Active Treatment[a]
Product Name	DDEA 2.32% Gel	DDEA 1.16% Gel	Placebo gel - 0% diclofenac gel
Pack Design	2 x 50 g tubes	4 x 50 g tubes	2 x 50 g tubes
Dispensing Details	1 kit per subject at Visit 1[a]	1 kit per subject at Visit 1[b]	1 kit per subject at Visit 1[a]
Product Master Formulation Code (MFC)	CCI [redacted]	CC [redacted]	CCI [redacted]
Dose/Application	Gel – 5 cm (2 g) on 200 cm^2	Gel – 5 cm (2 g) on 200 cm^2	Gel – 5 cm (2 g) on 200 cm^2
Route of Administration	Topical	Topical	Topical
Usage Instructions	Two times daily (BID) (morning and late afternoon)	Four times daily (QID)	Two times daily (BID) (noon and late evening)

[a] The study products for the Active Treatment and Placebo Product for Blinding of Active Treatment will be provided in a single kit containing 4 tubes (2 tubes of each study product)

[b] The study product for the Active Comparator will be provided in a single kit containing 4 tubes (4 tubes of Active Comparator product)

Rescue medication (paracetamol, up to 2000 mg daily) will be allowed during the study, except for the 6 hours prior to each study visit and 12 hours prior to Visit 3.

Type and Planned Number of Subjects

Approximately 300 subjects who present to the study within 24 hours of suffering a Grade I-II ankle sprain will be randomized to ensure at least 240 evaluable subjects complete the study for the (PP) per protocol analysis population.

Approximately 120 subjects per treatment arm has been determined to provide 80% power to demonstrate non-inferiority of DDEA 2.32% gel b.i.d with DDEA 1.16% gel q.i.d. by comparing the two-sided 95% confidence interval (CI) of the difference in mean change from baseline of VAS POM score between the two products with the non-inferiority margin of 13 mm. This assumes a treatment standard deviation of 22mm and allows for a possible small true treatment difference of 5mm in favor of DDEA 1.16%.

The primary efficacy endpoint will be the change from baseline in POM on Day 5 of treatment as assessed by a 100 mm VAS scale.

The following primary non-inferiority hypothesis will be tested for DDEA 2.32% vs DDEA 1.16%:

The null hypothesis is Diclofenac 2.32% DDEA Gel administered BID is inferior to Diclofenac 1.16% DDEA gel administered QID with the alternative hypothesis being Diclofenac 2.32% DDEA Gel administered BID is non-inferior to Diclofenac 1.16% DDEA gel administered QID.

Diclofenac 2.32% DDEA Gel administered BID will be declared non-inferior to Diclofenac 1.16% DDEA gel administered QID if the upper limit of the two-sided 95% CI of the difference between their mean changes from baseline VAS POM responses is less than the established margin of 13 mm.

1.1 Schedule of Activities

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

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening/Randomization (Baseline)	Study Period		
	Visit 1 Day 1	Visit 2 Day 3	Visit 3 Day 5	Visit 4 / Early D/C Day 8 ± 1
Written Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical History	X			
Demographics	X			
Current/Prior/Concomitant Medication Review	X	X	X	X
Subject Eligibility	X			
Physical Exam / Vital Signs (including height and weight)	X			X[h]
Urine Pregnancy Test[a]	X			X
Laboratory Safety Tests	X[b,c]			X[b,c]
Subject Continued Eligibility		X	X	X
Examination of Ankle Sprain	X			
Diagnostic Testing for Ankle	X[d]			
Ankle Swelling, Pain on Movement, Tenderness, Ankle Joint Function	X	X	X	X
Randomization	X			

Procedure/Assessment	Screening/Randomization (Baseline)	Study Period		
	Visit 1 Day 1	Visit 2 Day 3	Visit 3 Day 5	Visit 4 / Early D/C Day 8 ± 1
Adverse Events (AEs) Review	X[g]	X	X	X
Dispense Subject Diary	X	X	X	
Weigh Study Medication	X	X	X	X
Dispense Study Medication and Dosing Card	X			
Pain Intensity and Pain Relief (Diary)[e]	X	X	X	X
Apply Study Medication at Clinic by trained professional or nurse	X			
Dispense Rescue Medication	X		X[f]	
Review Diary		X	X	X
Count Rescue Medication		X	X	X
Collect Rescue Medication, Study Medication				X
Collect Diary		X	X	X
Study Conclusion/Subject Exit from Study				X

Footnotes:

[a] Women of child bearing potential

[b] Blood samples for chemistry and hematology

[c] Review results to ensure that there are no clinically significant abnormalities. Local laboratory will report results to center in order to allow the Investigator to review results no later than 24 hours after blood samples being taken

[d] As judged necessary by the investigator to exclude fracture of the ankle

[e] Denotes subject completion of diary components

[f] If necessary

[g] Adverse event collection commences from time of signed informed consent

[h] Height at Visit 1 only

2 INTRODUCTION

Ankle injuries are among the most common sports injuries [Fong 2007]. Eighty-five percent of ankle injuries are sprains, and of these, 85% are inversion sprains of the lateral ligaments [Rimando 2007]. A meta-analysis by Mason et al. of topical non-steroidal anti-inflammatory drugs (NSAIDs) considered sprains, strains and sport injuries, which includes ankle sprain, an appropriate model for acute pain conditions [Mason 2004]. Conventional forms of therapy for acute ankle sprain include use of NSAIDs, cryotherapy with cool packs, elevation of injured extremity, stabilization in a split plaster cast and bandaging [Stöckle 1997].

The efficacy and safety of topical NSAIDs in the treatment of acute, painful musculoskeletal conditions is widely recognized [Vaile 1998, Heyneman 2000, Mason 2004, Rainsford 2008, Zacher 2008]. Over the past 20 years, an increasing number of topical NSAID formulations (diclofenac, ibuprofen, indomethacin, ketoprofen, and naproxen) have been approved. A primary benefit of topically applied NSAIDs is that systemic absorption is only 3-8% of the total systemic absorption achieved with oral administration [Heyneman 2000], limiting the potential for systemic side effects characteristic of NSAIDs. Further advantages of topical delivery include circumventing the gastrointestinal tract and avoiding first-pass metabolism in the liver.

Pharmacokinetic studies have shown that diclofenamic acid, when applied topically, penetrates the skin barrier to reach joints, muscles and synovial fluid, in sufficiently high concentration to exert local therapeutic activity [Rademacher 1991]. The first topical Voltaren formulation, diclofenac diethylamine (DDEA) 1.16% gel (Voltaren Emulgel) has been marketed since 1985 worldwide for the relief of pain and inflammation associated with soft-tissue injuries, soft-tissue rheumatism and osteoarthritis as a three to four times daily application. Several clinical trials have been conducted with DDEA 1.16% gel supporting the efficacy and safety of the topical diclofenac formulation in the soft-tissue injuries, soft-tissue rheumatism, PPD and osteoarthritis indications [Niethard et al 2005, Zacher et al 2001]. Similarly, a 2.32% DDEA gel ,which is applied twice daily, has been approved worldwide for the same indications as the 1.16% DDEA gel since 2011. The twice a day topically administered regimen has demonstrated efficacy in relief of acute pain resulting from soft tissue injuries as observed in study [VOPO-P-307][Predel et al 2012]. The global clinical study data in conjunction with the extensive post marketing experience, provide robust evidence of the safety and efficacy of both the marketed DDEA gel formulations.

2.1 Study 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, and generic name of DDEA Emulgel was registered in China) 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 42 countries.

As part of the global expansion for the product, China has been identified as a desirable market for registration of DDEA 2.32% gel. The identified registration pathway for the DDEA 2.32% gel is variation specifying addition of a new strength to the already registered DDEA 1.16% gel (License Number H20181225/H20181226, firstly issued on March 12, 2013), with the same indications

as currently registered for DDEA 1.16% gel, i.e. for the relief of mild to moderate pain in muscles, soft tissues, and joints, e.g. muscles or soft tissue pains caused by sprain, pulling injury, contusions, strain, waist-back injury and various arthralgia etc, and for symptomatic treatment of osteoarthritis.

In support of the proposed registration, the National Medical Products Administration (NMPA) approved a clinical trial application (CTA) on November 06, 2016 (CTA No. 2016L09875). The approved CTA stipulated that a non-inferiority study assessing the efficacy and safety of the DDEA 2.32% versus that of the registered DDEA 1.16% should be conducted in a local population.

To this effect, GSKCH intends to conduct a randomized, double blind, multi-center, active controlled, parallel group, non-inferiority study to evaluate the efficacy and safety of DDEA 2.32% gel applied twice daily versus DDEA 1.16% gel applied four times daily in subjects with ankle sprain in China.

Ankle sprain is a common and well defined joint injury involving the soft tissues. A significant proportion of subjects experience strong pain and functional impairment without appropriate treatment options. The DDEA 2.32% gel offers the opportunity to provide a safe and effective treatment while improving subject treatment compliance and convenience.

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

2.2 Background

DDEA 2.32% gel corresponds to 20 mg of diclofenac sodium in 1 g of gel. DDEA 2.32% gel has been developed as a higher-strength formulation of the well known globally marketed Voltaren Emulgel (DDEA 1.16% gel) and is approved for the same indications as DDEA 1.16% gel, i.e.: 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);
- Localized forms of soft tissue rheumatism: tendonitis (e.g. tennis elbow), bursitis, shoulder-hand syndrome and periarthropathy;

And for the relief of pain of non-serious arthritis of the knee or fingers.

The twice a day topically administered regimen has demonstrated efficacy in relief of acute pain resulting from soft tissue injuries as observed in study VOPO-P-307, where the twice daily regimen showed a statistically significant reduction in pain as compared to placebo 5 days after injury. The DDEA 2.32% gel is designed to achieve efficacy with less frequent daily applications as compared to the DDEA 1.16% gel, thereby potentially improving treatment compliance and convenience for the subject. To date, the safety profile of the DDEA 2.32% gel has proven to be similar to that of the DDEA 1.16% gel (CCI).

When applied to the skin, DDEA 2.32% gel achieves penetration by the active ingredient, diclofenac, into the target tissues with low systemic exposure (PPD and PPD). In addition to containing double the concentration of active ingredient compared with the originator product DDEA 1.16% gel, DDEA 2.32% gel employs a permeation enhancer, 0.75% oleyl alcohol, to meet the target permeation level. Oleyl alcohol is commonly used in dermal products and is known to be well tolerated.

As part of the development program for DDEA 2.32% gel, a series of preclinical studies compared the DDEA 2.32% gel formulation with the marketed DDEA 1.16% gel formulation. An *in vitro* skin permeation study was performed to evaluate the delivery of diclofenac from DDEA 2.32% gel. The study showed that diclofenac penetration rates were approximately three times greater for DDEA 2.32% gel than for DDEA 1.16% gel.

2.3 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 global Indication (CCI [redacted]) for DDEA 1.16% and 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);
- Localized 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."

Similarly, the approved indication in China for DDEA 1.16% is:

For the relief of mild to moderate pain in muscles, soft tissues, and joints, e.g. muscles or soft tissue pains caused by sprain, pulling injury, contusions, strain, waist-back injury and various arthralgia etc. and for symptomatic treatment of osteoarthritis.

3 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to demonstrate non-inferiority between DDEA 2.32% and DDEA 1.16% with regard to pain relief after acute ankle sprain.

The primary and secondary endpoints are detailed in Table 3-1.

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To demonstrate non-inferiority between DDEA 2.32% and DDEA 1.16% with regard to pain relief after acute ankle sprain	Change from baseline in pain on movement (POM) on Day 5 of treatment as assessed by a 100 mm VAS scale
Secondary	
To assess safety of DDEA 1.16% and DDEA 2.32% gels after 1 week of use	Number, incidence, and severity of adverse events following dosing with study medication
To assess efficacy of treatments for pain relief as measured by POM on Days 3 and 8	Change from baseline of POM on VAS on Day 3 and Day 8 of treatment assessed by 100 mm VAS scale
To assess efficacy of treatments for inflammation of the affected ankle as measured by pressure algometry on Days 3, 5, and 8	Change from baseline in tenderness as measured by pressure algometry on Days 3,5 and 8
To assess efficacy of treatments for inflammation of the affected ankle as measured by pressure algometry on Days 3, 5, and 8	Difference between measurement in affected ankle and contralateral ankle on Days 3,5 and 8

To assess efficacy of treatments for ankle joint function as measured on the Karlsson Scoring Scale	Change from baseline in Ankle Joint Function (Karlsson Scoring Scale) on Days 3,5 and 8
To assess efficacy of treatments for swelling of affected ankle as measured Figure of Eight Method	Change from baseline in circumference of affected ankle as measured by Figure of Eight method on Days 3,5 and 8
To assess efficacy of treatments for swelling of affected ankle as measured by Figure of Eight method	Difference between circumference of affected ankle to unaffected ankle by Figure of Eight method on Days 3, 5 and 8
To assess efficacy of treatments for effect on pain intensity as measured by Sum of Pain Intensity Difference (SPID)	SPID from 0 – 24 hours post first dose (Day 1) and from 96 – 120 hours post first dose (Day 5)
To assess effect of treatments for effect on pain relief as measured by Total Pain Relief (TOTPAR)	TOTPAR from 0 – 24 hours post first dose (Day 1) and from 96 – 120 hours post first dose (Day 5)
To assess the use of rescue medication among subjects	Number of tablets usedto treat ankle pain and overall
To assess the use of rescue medication among subjects	Number of days on which rescue medication was used to treat ankle pain and overall

This study will be considered successful if the primary objective is met; i.e. that DDEA 2.32% is non-inferior in terms of change from baseline in pain on movement after acute ankle sprain as compared to DDEA 1.16% on Day 5.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase III, randomized, double blind, multi-center, active controlled, 2-treatment arm, parallel group, non-inferiority study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice daily versus diclofenac diethylamine 1.16% gel applied four times daily for 1 week in subjects with acute ankle sprain.

To qualify, subjects must experience an acute Grade I -II sprain of the ankle within the past 24 hours and experience pain on movement of at least 50 mm on a 100 mm VAS scale. Subjects should be randomized as soon as possible after the injury.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the following two treatment arms:

Table 4-1 Treatment Schedule

Treatment Arms	Morning (Upon Rising)	Noon	Late Afternoon (evening)	Late Evening (bed time)
DDEA 2.32% four times daily	DDEA 2.32% gel	Placebo gel	DDEA 2.32% gel	Placebo gel
DDEA 1.16% four times daily	DDEA 1.16% gel	DDEA 1.16% gel	DDEA 1.16% gel	DDEA 1.16% gel

Approximately 300 subjects (150 in each group) with acute ankle sprain are to be randomized. All subjects will receive four (4) tubes of study drug, for treatment in morning, noon, late afternoon, and late evening, respectively. The very first dose of study drug will be applied at

the study center. The subjects will be instructed to apply the gel topically with the finger tips for approximately 1 minute in the morning, at noon, late afternoon, and late evening for 7 days. Each tube will be labeled for use at one of these 4 times.

After the randomization visit (Visit 1/baseline visit), subjects will return to the study site for post baseline visits, namely Visit 2, Visit 3, and Visit 4 to complete efficacy and safety assessments. Baseline safety laboratory test blood samples will be taken at Visit 1. End of study safety laboratory tests will also be taken at Visit 4, or in case of early termination. In addition, subjects (ex clinic) will assess pain intensity and pain relief at frequent intervals on Day 1 and then at each study drug application throughout the rest of the study. The schedule of visits is described below.

Study center visits per subject:

Screening / Randomization visit [Visit 1]	Day 1 (0 h)
1st interim visit [Visit 2]	Day 3 (48 ± 4 h after initiating treatment)
2nd interim visit [Visit 3]	Day 5 (primary endpoint measurement) (96 ± 4 h after initiating treatment)
Final visit [Visit 4]	Day 8 ± 1 d (7 ± 1 days after initiating treatment)

Rescue medication (paracetamol, up to 2000 mg daily) will be allowed during the study, except for the 6 hours prior to each study visit and 12 hours prior to Visit 3.

4.2 Rationale for Study Design

As discussed in Section 2.2 and Section 2.3, DDEA 1.16% and DDEA 2.32% are registered globally for the relief of pain, swelling and inflammation from a variety of musculoskeletal conditions. There is an extensive body of clinical study and post marketing experience to support the efficacy of both the DDEA 1.16% and 2.32%. Part of the rationale for conducting this study is to reproduce the efficacy and safety of the products in a Chinese population.

The DDEA 1.16% gel is currently marketed in China. As described in Section 2.1, in order to expand the global footprint of the DDEA 2.32% gel to China, a local study is required. The design stipulated in the NMPA approved CTA is a non-inferiority study design versus the approved DDEA 1.16% active comparator. This is considered an appropriate design when there is extensive evidence of efficacy and safety of the active comparator and the aim is to leverage this existing evidence by demonstrating that a new product which can offer advantages, such as improved compliance and convenience, would result in no important loss of efficacy versus the active comparator. The DDEA 1.16% has demonstrated consistent and reproducible efficacy as compared to placebo in both acute and chronic clinical pain models. Moreover, this is especially applicable to the current situation as the test product, DDEA 2.32%, has also demonstrated efficacy in a placebo-controlled trial.

Given the extensive global evidence of safety and efficacy in both the active comparator and test arms, the important contribution resulting from the conduct of the non-inferiority trial is to demonstrate no important loss of efficacy from the approved active comparator in a local population.

4.3 Justification for Dose

The dose for the active comparator DDEA 1.16% will be an application of 5 cm of gel (equivalent to approximately 2 g of gel and as determined by a provided dosing card) to both sides of the affected ankle four (4) times daily. This is consistent with the approved labeled dose for DDEA 1.16% in China.

Globally, the labeled approved dose for DDEA 2.32% is an amount of 2 – 4 g of gel (roughly the size of a cherry or walnut) applied twice daily. To produce a more uniform dose for the purpose of the trial and to provide recommendations more in line with the approved labeled dose of the DDEA 1.16% in China, the dose for the trial for the DDEA 2.32% will be an application of 5 cm of gel (equivalent to 2 g of gel and as determined by a provided dosing card) to both sides of the affected ankle two (2) times daily. For subjects receiving DDEA 2.32% gel, placebo gel will be administered in the same fashion two (2) times daily to maintain blinding.

Based on previous experience it is expected that measurement of pain and disability over approximately one week would adequately characterize the profile over time of the analgesic effect of both DDEA 1.16% and DDEA 2.32% (Mason, et al 2004, Predel, et al 2004).

To minimize unnecessary risks to subjects during study participation subjects will be screened at baseline to ensure absence of the various clinical disorders described in the exclusion criteria. This comprehensive process consists of a baseline physical examination, vital signs, medical history and drug history. Safety laboratory blood samples for chemistry and hematology will also be taken at the baseline visit before subjects are randomized to study treatment, and their results will be reviewed as early as possible.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The end of this study is defined as the date of the last visit or the last scheduled procedure of the last subject in the study.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomize approximately 300 subjects to ensure at least 240 evaluable subjects complete the study without any major protocol deviations. Healthy adults 18 – 75 years old who present to clinic within 24 hours of sustaining a grade I or II lateral ankle sprain (as assessed by the investigator) and experience pain on movement of at least 50 mm on a 100 mm VAS scale will be enrolled into the study.

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 non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

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

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 and 75 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan and other study procedures.
4. Acute sprain of the lateral ankle on one side only, Grade I-II [Wolfe 2001]
5. Pain-on-movement ≥ 50 mm on a 100 mm VAS
6. Injury within the past 24 hours before randomization
7. No pain medication may have been taken within the 24 hours that precedes randomization. Treatment by rest, ice, compression, or elevation (RICE) is authorized prior to randomization. Stable daily doses of acetylsalicylic acid (≤ 162 mg) taken for at least 30 days prior to the first dose of study medication for non-analgesic reasons may be continued for the duration of the study.
8. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee with no clinically significant/relevant abnormalities in medical history or upon physical examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
9. Female subject of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 14 days after the last dose of assigned treatment. A female subject who is of childbearing potential must meet requirements in Section 5.5.4.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrollment into the study:

1. During the past 3 months: Grade I – III sprain of the affected ankle
2. During the past 6 months: Grade II – III sprain, any other significant injury (such as fracture or torn ligament), or surgery (except for skin or nails) of the affected ankle or foot.
3. Pain or instability in the affected ankle attributable to previous ankle sprain or any other trauma.
4. Ankle sprain attributable to a known disease affecting the ligaments, such as ligament hyperlaxity due to connective tissue diseases (e.g. Marfan's syndrome, Down's syndrome, Ehlers – Danlos syndrome).
5. Any skin lesion or wound in the area to be treated
6. Intent to undergo surgery during time of participation

7. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
8. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical, including other current acute or chronic pain conditions, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
9. A subject who is a pregnant female.
10. A subject who is a breastfeeding female.
11. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
12. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
13. A subject unwilling or unable to comply with the Lifestyle Considerations (Section 5.5) described in this protocol.
14. A subject who has made use of prescription, non-prescription, or dietary supplements, containing NSAIDs, COX-2 inhibitors and other analgesic treatments within 7 days or 5 half-lives, whichever is longer, prior to the first dose of investigational product and during the study.
15. Topical analgesics or anti-inflammatory treatment over the previous 30 days in the area to be treated in the study period
16. A subject with evidence of clinically significant laboratory abnormality caused by renal disease (Serum creatinine ≥ 1.5 times the upper limit of normal (ULN)), hepatic disease (ALT or AST ≥ 2 times the ULN), or subject with allergic disease at screening that may increase the risk associated with study participation.
17. A subject with 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.
18. A subject who has received treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).
19. A subject who has previously been enrolled in this study.
20. Any physical impairment that would influence the study's efficacy evaluations, in particular POM and the ankle joint function, such as : peripheral or central neurological disease, significant back pain, symptomatic osteoarthritis of the hips, knees or feet, or any painful conditions of the lower extremities (e.g. painful nail, wound, corn, or wart).

5.4 Randomization Criteria

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

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

- No special requirement for food and drink prior to safety laboratory evaluations.

5.5.2 Alcohol, Caffeine and Tobacco

- Subjects will abstain from caffeine-containing products for 12 hours prior to study visit days (except screening/randomization visit).

5.5.3 Activity

- Subjects will abstain from strenuous exercise (e.g. heavy lifting, weight training, calisthenics, aerobics) for the duration of the study. Walking at a normal pace will be permitted.

5.5.4 Contraception

Female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use at least one highly effective method of contraception consistently and correctly for the duration of the active study period and for at least 14 days after the last dose of investigational product.

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 addition, the investigator or 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 or the subject's partner.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy that meets the GSK definition (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of reproductive potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher 2007])
4. Injectable progestogen [Hatcher 2007]
5. Contraceptive vaginal ring [Hatcher 2007]
6. Percutaneous contraceptive patches [Hatcher 2007]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher 2007]. The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. 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.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, and any adverse events or incidents as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, investigational product is defined as a pharmaceutical form of an active ingredient, a non-medicinal product (marketed or investigational), or a placebo, being tested or used as a reference (positive or negative control), in a clinical trial. This includes 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.

6.1 Investigational/Study Product Supplies

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Investigational/Study Product Supplies

	Active Treatment[a]	Active Comparator[b]	Placebo Product for Blinding of Active Treatment[a]
Product Name	DDEA 2.32% Gel	DDEA 1.16% Gel	Placebo gel - 0% diclofenac gel
Pack Design	2 x 50 g tubes	4 x 50 g tubes	2 x 50 g tubes
Dispensing Details	1 kit per subject at Visit 1[a]	1 kit per subject at Visit 1[b]	1 kit per subject at Visit 1[a]
Product Master Formulation Code (MFC)	CCI [redacted]	CC [redacted]	CCI [redacted]
Dose/Application	Gel – 5 cm (2 g) on 200 cm^2	Gel – 5 cm (2 g) on 200 cm^2	Gel – 5 cm (2 g) on 200 cm^2
Route of Administration	Topical	Topical	Topical
Usage Instructions	Two times daily (BID) (morning and late afternoon)	Four times daily (QID)	Two times daily (BID) (noon and late evening)
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned	All used/unused samples to be returned
Storage Requirements	Store below 25°C	Store below 25°C	Store below 25°C

[a] The study products for the Active Treatment and Placebo Product for Blinding of Active Treatment will be provided in a single kit containing 4 tubes (2 tubes of each study product)

[b] The study product for the Active Comparator will be provided in a single kit containing 4 tubes (4 tubes of Active Comparator product)

Table 6-2 Rescue Medication Information

	Rescue Medication
Product Name	500 mg paracetamol tablets
Pack Type	Pack of tablets
Dispensing Details	Dispense at Visit 1. May re-dispense at Visit 3 if necessary.
Product Formulation Code	Commercial product
Dose	One 500 mg tablet with water per dose. May be repeated after 4 hours. Maximum daily dose 2000 mg.
Route of Administration	Oral
Usage Instructions	As needed for pain
Return Requirements	All used/unused samples to be returned
Storage Requirements	Store sealed.

Table 6-3 Sundry Items

Sundry Items to be supplied:

Item Name	Supplied By	Pack Type	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Urine pregnancy test	GSK/CRO/Site*	Unit	To be used by site staff at visit 1	Dispose at site	Return
Dosing Card	GSK	Each	Included in treatment kit	Return	Return
Subject Diary	CRO	Each	To be provided to subjects	Return	Return

* CRO = Contract Research Organization

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSK CH during the course of the study in time for study close out visit.

6.1.1 Dosage Form and Packaging:

DDEA 2.32%, DDEA 1.16%, and placebo gels will be supplied to the clinical site as packaged tubes for dispensing by the pharmacy.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

All products supplied are for use only in this clinical study and should not be used for any other purpose. Subjects must not exchange their designated products with other study subjects.

6.1.2 Preparation and Dispensing

DDEA 2.32% gel, DDEA 1.16% gel, and placebo will be prepared and/or dispensed by qualified site personnel according to the dosage and administration instruction.

Once the eligibility of a subject has been confirmed, the Investigator (or nominated assistant) should contact the IVRS/IWRS Centralized Randomization Centre for allocation of randomized therapy.

The actual treatment given to individual subjects will be determined by a randomization scheme that has been loaded into the (IVRS/IWRS) database. Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSK CH vendor, using validated software.

All subjects will be identified to the Centralized Randomization Centre using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided to each site.

The IVRS/IWRS Centralized Randomization Centre will inform the investigator of the Kit ID number to be allocated to the subject after subjects become eligible for randomization.

6.2 Administration

All subjects will be given 4 tubes of study drug and the same usage instructions. Subjects should spread a total of approximately 2 grams of study medication (using the dosing card) on both sides of the ankle. The study drug should be applied topically with the fingertips to both sides of the affected ankle for approximately 1 minute (corresponds to a region of approximately 200 cm^2). After application, the hands should be washed. On Day 1, to demonstrate proper application, the first dose of study drug will be applied at the study center from the morning tube (regardless of the time of randomization). Subsequent doses will be applied from the tube associated with the corresponding time of day separated by at least 3 hours (i.e. if the first dose is applied at 15:00 hr from the morning tube, the next dose will be at approximately 18:00 hr from the late afternoon tube and the next dose will be at approximately 21:00 hr from the late evening tube). All 4 doses of study drug should be applied on Day 1, if possible, preferably with at least 3 hours between doses. If this is not possible, at a minimum 3 doses should be administered with at least 3 hours between doses.

The subjects will be instructed to continue to apply the gel topically with the fingertips four times a day for 7 days. Dosing times should be distributed as evenly as possible over the day, preferably once upon first arising (i.e., after washing or shower or bath), once at lunch (approximately 12:00 hour), once in the late afternoon (approximately 17:00 hour), and once in the late evening (i.e., after washing approximately 21:00 hour). There should be a period of at least 4 hours between individual applications. The appropriately-labeled tube should be used for each application.

Subjects can take a shower or bathe prior to application. Subjects should not shower, bathe or wash the treated area within the first three hours after the application. Subjects should wash their hands after use and should wait 10 minutes before covering the treated skin with clothing.

The investigator will instruct the subject to take the study drug exactly as prescribed and state that compliance is necessary for the subject's safety and the validity of the study. The subject will be told to contact the investigator if he/she is unable for any reason to take the gel as directed/prescribed. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Any missed or skipped doses must be recorded in CRF.

Subjects will be instructed to self-administer their assigned product per the above usage instructions which will be explained and provided to the subject.

6.2.1 Medication/Dosing Errors

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

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

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

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

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

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

6.3 Investigational/Study Product Storage

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

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

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

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

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

6.4 Investigational/Study Product Accountability

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

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the study staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels (Table 6-1,Table 6-2) . Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

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

All unused product must be returned at the final Visit 4. 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.

6.4.1 Destruction of Investigational/Study Product Supplies

At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including emptying containers) will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

6.5 Blinding and Allocation/Randomization

At Visit 1, 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. 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. 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 1:1 ratio, with equal numbers receiving DDEA 2.32% + Placebo gel and DDEA 1.16% gel. Randomization numbers will be assigned to individual centers in order to stratify the randomization by center.

Before the study is initiated, training, login information and directions for the IRT will be provided to each site. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits.

Returned study products should not be re-dispensed to any subject.

The investigator's knowledge of the product allocation should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

This study is described as double-blind (the subjects and clinical examiner will be blinded to the product received). The study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the sponsor, who may influence study outcomes will also be blinded to the product allocation. The placebo gel and active gels will be identical in packaging, labeling, odor, schedule of administration, and as identical as possible in appearance.

To ensure the examiner remains blinded throughout the study, staff involved in the preparation, dispensing, and application of study products will work in a separate area. The examiner is not permitted in any area where study product is stored, dispensed, or in use.

Subjects will be instructed not to remove study products from the opaque bags provided outside of the dispensing room, while at the study site. Dispensing staff and staff supervising administration of IP will not be involved in any efficacy/safety assessment procedures during the study.

Randomization data will be kept strictly confidential, 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.

6.6 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 an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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

6.7 Subject Compliance

The first dose of study products will be administered by investigator site personnel in order to demonstrate proper application of the treatments.

The subject will return the trial medication (used or unused) at every visit and the investigator will record the number of study drug applications for each tube separately for morning, noon, late afternoon and late evening in the CRF. The returned tubes will be weighed with the cap and the weight will be recorded in mg on the drug accountability form in the CRF. Applying 2 g per use, the weight of each tube will decrease by approximately 2 g each study day.

If it appears that the subject used too little or too much study drug, the subject will be re-instructed about the correct application technique by the investigator or the study nurse.

At the last visit, the subject will return the tubes to the investigator who will store them until the monitor arranges for their return. The investigator must not destroy any drug.

In addition, a diary will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects at each visit and transcribed to the CRF as appropriate.

6.8 Subject Diary

A diary will be handed out to the subject at Visit 1,Visit 2, and Visit 3.

- Every time gel is applied, the subject must document the time and date of application. This includes gel applied at the clinic site
- Pain intensity and pain relief will both be assessed by the subjects every 2 hours ± 30 minutes (after starting study drug) until the subject goes to bed on the evening of Day 1. The same assessment and recording frequency will also be followed starting with the first dose on Day 5. On Day 1 and Day 5 where an assessment time point coincides with a dosing time point, the assessment of pain intensity and pain relief should be made prior to the dose. For all other time periods, pain intensity and pain relief will be assessed and recorded immediately prior to each study drug application.
- Every time rescue medication is taken (not allowed within 6 hours of Study Visits and within 12 hours of Study Visit 3), the subject must document:
    - Time and date of rescue medication
    - Number of tablets taken
    - Reason for use of rescue medication
    - Pain intensity and pain relief immediately prior to each dose of rescue medication

The Investigator or designee will ensure that all diary entries completed by the subject are legible. The Investigator will review the diary at each clinic visit. The diary handed out to subjects on Visit 1, Visit 2, and Visit 3 will be collected by the Investigator or designee at Visit 2, Visit 3, and Visit 4 (Day 8±1) respectively.

6.9 Concomitant Medication/Treatment(s)

As a general rule, no concomitant medications should be taken 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 up to Visit 4– as these are the basis for subject exclusion.

Concomitant therapies prohibited during the study:

• Analgesics since the injury, administered by any route (i.e., topical, oral, rectal, injected, or inhaled), except rescue medication as described in Section 6.10, and acetylsalicylic acid taken for at least 30 days on a stable daily dose (≤ 162 mg) for non-analgesic reasons. Pain medication taken prior to the injury must be washed out for at least 24 hours before randomization. The following concomitant medications and/or therapies are prohibited:

- Systemic or topical NSAIDs;
- Steroids (injected or oral, except inhaled topical asthma and hayfever treatments and topical dermal treatments not applied to the sprained ankle);
- Physiotherapy (including, but not exclusive to, transdermal electro neural stimulation (TENS), ultrasound, massage, and spinal manipulation) or any other kind of pain therapy throughout the course of the study;
- Tranquilizers, anxiolytics, hypnotics, or sedatives, unless the subject's prescribed daily dose has been unchanged for a month before the randomization visit; this regimen must continue unchanged for the entire study;
- Amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine, and tetrahydrocannabinol;
- Traditional, herbal or homeopathy treatments (oral and topical);
- Adhesive and/or immobilizing casts, bandages, Aircast splints, treatment by rest, ice, compression, or elevation (RICE) are not allowed.

Subjects will receive paracetamol as rescue medication as described in Section 6.10. Use of a crutch and certain physician approved exercises will be allowed. The physician will instruct the subject to start Achilles' tendon stretching on Day 1.

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication/treatments at each site visit.

Medication/treatments taken within 90 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after signing the informed consent form will be documented as concomitant medication/treatments.

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.

6.10 Rescue Medication

The investigator will provide rescue medication (paracetamol, 500 mg tablets) to the subject at the baseline visit. Rescue medication will be re-dispensed on Day 5 (V3), if necessary.

Subjects will be instructed to take only the rescue medication provided for pain in the ankle or any other pain (e.g., headache) or fever (e.g., due to common cold) they might experience during the trial. One tablet may be taken, repeated after at least 4 hours, if needed, up to a maximum of 2000 mg (four tablets) per day. No rescue medication is allowed within 6 hours prior to the study visits or within 12 hours of Study Visit 3.

The subject will receive a Subject Diary at Visit 1, Visit 2, and Visit 3 to record the information described in Section 6.8. At each visit, the investigator or designee will review the rescue medication use recorded in the diary and will transfer the relevant information to the CRF. Empty packages and rescue medication not used will be returned to the investigator. The investigator or designee will then compare the packages vs. the subject's rescue medication form and any discrepancies will be noted in the CRF.

The investigator will further investigate any instances in which rescue medication was taken for reasons other than ankle sprain and complete the Adverse Event Form, if appropriate.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

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

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

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

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

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

If the subject withdraws from the study and 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.

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening / Randomization Visit

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

As subjects must enter the study and receive treatment within 24 hours of injury, subjects will be screened and randomized within 24 hours prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures will be completed:

8.1.1 Informed Consent

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

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

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

The time the subject signed the informed consent form will also be captured on the Informed Consent Form as this is the point at which all Adverse Events will be captured from. The date and time of consent will be transcribed to the CRF.

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

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race.

As an important aspect of the trial is that it be conducted in a local population, race, is an important element in establishing a representative population.

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be reviewed and documented in the CRF.

8.1.4 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 5 years), including allergies or drug sensitivity, will be documented in the CRF. Of specific interest are diseases of the affected ankle or foot in the last 6 months and any concurrent injuries concerning the lower extremities.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 90 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.5 Subject Eligibility

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

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines (Section 5.5) and any Concomitant Medication/Treatment(s) (Section 6.9) requirements of the protocol.

8.1.6 Screening/Randomization Procedures

The following additional procedures will occur at the Screening/Randomization visit:

- Examination of ankle sprain

- POM, tenderness, ankle swelling, and ankle joint function (total score and subcategories) will be assessed
- General physical examination including vital signs, weight, and height. Urine pregnancy test (women of child bearing potential only)
- Safety laboratory blood samples for chemistry and hematology
- Eligible subjects receive a randomization number
- Baseline Pain Intensity and Pain Relief recorded in CRF
- Study medication will be weighed and dispensed to the subject. The weight of each tube will be documented in the CRF. The dosing card will also be provided to the subject.
- The investigator or a study nurse/doctor's assistant will apply the first dose of study drug at the study site from the morning tube, and the subject will be instructed in application amount, method, and time. The subject will also be shown how to utilize the dosing card. Four (4) doses of study drug should be applied in total on Day 1, with a minimum of 3 hours between each dose.
- Dispense Visit 1 subject diary and instruct subject about appropriate use
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel" will be assessed and any AEs recorded in the CRF.
- Rescue medication will be dispensed and subjects will be instructed on appropriate use

8.2 Study Period

Remind subject to inform the site if they experience any untoward medical occurrence or use any medications in the next 2 days.

8.2.1 Visit 2/Day 3

- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF. Review safety laboratory tests for chemistry and hematology. Having received the results from the samples taken at Visit 1 before the subject attends for Visit 2, the Investigator will review the results to ensure that there are no clinically significant abnormalities. Any subject with clinically significant abnormalities which in the assessment of the investigator are reason for withdrawal will be withdrawn from the study at Visit 2 and procedures described for Visit 4 will be completed. Any subject with a clinically significant abnormality will be followed until its resolution.
- Subject continued eligibility
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.
- The 4 tubes of study medication will be weighed. The weight of each tube will be documented in the CRF.
- Review Visit 1 Diary
    - Review time and date of each gel application
    - Review scores for Pain Intensity and Pain Relief
    - Review rescued medication use.

- POM, tenderness, ankle swelling, and ankle joint function (total score and subcategories) will be assessed
- Count and document remaining rescue medication
- Collect Visit 1 subject diary
- Dispense Visit 2 subject diary and instruct subject about appropriate use

8.2.2 Visit 3/Day 5

- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.
- Subject continued eligibility
- The 4 tubes of study medication will be weighed. The weight of each tube will be documented in the CRF.
- Review diary
    - Review time and date of each gel application
    - Review scores for Pain Intensity and Pain Relief
    - Review rescued medication use.
- POM, tenderness, ankle swelling, and ankle joint function (total score and subcategories) will be assessed
- Count and document remaining rescue medication.
- If insufficient rescued medication remains, additional rescue medication may be dispensed
- No rescue medication is allowed within 12 hours of this Visit
- Collect Visit 2 subject diary
- Dispense Visit 3 subject diary and instruct subject about appropriate use

8.2.3 Visit 4 /Day 8 ± 1

Procedures for this visit are also to be completed if the subject terminated the study prematurely.

- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.
- Subject continued eligibility
- The 4 tubes of study medication will be weighed. The weight of each tube will be documented in the CRF
- Collect remaining study medication and rescue medication
- Review diary
    - Review time and date of each gel application
    - Review scores for Pain Intensity and Pain Relief
    - Review rescued medication use.
- Collect Visit 3 subject diary
- Perform a general physical examination including vital signs

- Urine pregnancy test (women of child bearing potential only)
- Safety laboratory blood samples for chemistry and hematology. Any subject with a clinically significant abnormality will be followed until its resolution.
- POM, tenderness, ankle swelling, and ankle joint function (total score and subcategories) will be assessed
- Count and document remaining rescue medication

8.3 Study Conclusion

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

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

8.4 Follow-up Visit / “Phone Call”

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

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol. For individual subjects, the examiner should remain consistent throughout the study period where possible.

The following chronological sequence will be observed for the assessments below:

1. Ankle swelling

2. Pain on movement

3. Tenderness

9.2.1 Ankle Swelling

Ankle swelling is evaluated at Visits 1-4 by the Figure-of-eight-method, a common procedure to assess ankle size. The method has been validated on healthy volunteers with an intra-class correlation coefficient of 0.99 for inter-tester reliability and 0.99 for intra-tester reliability [Tatro Adams 1995, Petersen 1999, Friends 2008].

The Figure-of-eight-method is reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling.

In detail: a one-quarter-inch wide (about 63 mm), retractable, plastic tape measure is utilized to obtain the measurements of each subject's ankle. All measurements are recorded in cm. Each subject is seated comfortably in a long sitting position with both feet extended beyond the end of the plinth in a slight dorsiflexion position. The figure of eight-method is applied to both feet and the tape measure is wrapped around the ankle along the following course: the beginning of the tape is placed midway between the tibialis anterior tendon and lateral malleolus and is then continued across anatomically defined points in the form of a figure of eight around the ankle joint (for details [Tatro Adams 1995]). The tape localization of the first measurement should be marked with an appropriate marker.

Each ankle is measured three times and the average is calculated. The difference in this average between ankles tracks the natural course of disease.

9.2.2 Pain on Movement

The investigator will perform a manipulation of the ankle (i.e., movement) (described below), and the pain assessment will be done by the subject. These will occur at the study center on Days 1, 3, 5 and 8 (±1) (Visits 1–4) using a 100 mm VAS.

The manipulation will be performed as follows:

The subject is asked to lie down on an even horizontal surface. The investigator gently lifts the leg and holds it up in the air at an angle of approximately 45°. While holding the leg with one hand, the investigator performs a gentle inversion (i.e., supination) of the foot of the injured ankle to reach an angle of approx. 30°.

The extent of ankle pain is evaluated by the subject in answer to the question:

"How would you describe your ankle pain right now?"

The pain-on-movement is registered by the subject by drawing a perpendicular line on the 100 mm VAS scale with anchors at 0 = "no pain" and 100 = "extreme pain".

9.2.3 Tenderness

'Tenderness' is the sensation of pain expressed by a subject when pressure is applied to the body. A more precise term is 'pressure pain threshold', the minimum pressure required to cause pain. Tenderness or pressure pain threshold is one of the major palpatory signs used by practitioners for diagnostic and treatment assessment purposes. Tenderness can be quantified with an algometer (pressure pain meter). It measures the amount of pressure a subject can endure before a pain sensation is elicited. Algometers have been used extensively to measure the efficacy of therapeutic interventions for the treatment of pain [Fischer 1987, Ohrbach 1989, Galer 2000,

Wetzel 2002, Chesterton 2003]. The reliability of repeated measurements of pressure pain threshold has been demonstrated [Fischer 1987, Nussbaum 1998].

Tenderness will be measured by calibrated algometers in an area of 1 cm^2 at the centre of the injured area. The position of measurement will be marked with a water resistant marker on subjects' skin to ensure consistent measuring points throughout the study. The investigator will apply the pressure gauge to the marked tender point of maximum sensitivity by placing the gauge at a 90° angle vertical to the skin.

The subject is instructed to indicate the onset of pain (pressure pain threshold) with a verbal cue such as "Yes" or "Stop". Measurements will be performed with covered scale so that investigator and subject cannot see the values. They will be evaluated after measurement.

For assessment of a treatment effect the tenderness of the treated painful area has to be compared with the tenderness at the corresponding anatomical position of the healthy uninjured contralateral side.

9.2.4 Ankle Joint Function

Evaluated by the subject at the study center at Days 1, 3, 5 and 8 (±1) (Visits 1-4) using the Karlsson Scoring Scale [Karlsson 1991 and 1996]. This validated scoring scale measures recovery of ankle joint function after an acute ligament injury. Assessments are made in the following eight categories (score): pain (20), swelling (10), instability (subjective) (15), stiffness (5), stair climbing (10), running (10), work activities (15), and the use of a support device (5). The total score ranges in value from 0 to 90.

9.2.5 Diary Pain Intensity and Pain Relief Assessments

Pain intensity will be assessed in the diary on a 4-point categorical scale.

"How would you describe your ankle pain right now?"

0 = "no pain", 1 = "mild pain", 2 = "moderate pain", 3 = "severe pain".

Spontaneous pain relief will be assessed in the diary on a 5-point categorical scale.

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

0 = "no relief"; 1 = "a little relief"; 2 = "some relief"; 3 = "a lot of relief "; 4 = "complete relief".

Pain intensity and spontaneous pain relief will both be assessed at baseline (immediately prior to first dose) and every 2 hours ± 30 minutes (after starting study drug) until the subject goes to bed on the evening of Day 1. The same assessment and recording frequency will also be followed starting with the first dose on Day 5. On Day 1 and Day 5 where an assessment time point coincides with a dosing time point, the assessment of pain intensity and pain relief should be made prior to the dose. For all other time periods, pain intensity and pain relief will be assessed and recorded immediately prior to each study drug application.

9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.3.1 Laboratory Tests

The following laboratory tests/analytical measures will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

Table 9-1 Laboratory Tests

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose Calcium Magnesium Sodium Potassium Chloride Total CO2(Bicarbonate) AST, ALT Direct Bilirubin Indirect Bilirubin Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein PT/INR	Urine pregnancy test

Definitions: RBC= Red blood cell; WBC= White blood cells; BUN=Blood urea nitrogen; AST= transaminase; ALT= alanine transaminase; PT/INR= prothrombin time/ international normalized ratio.

Information on the local laboratory and sampling routines, normal ranges, and reporting will be provided in the Investigator binder supplied to each center. The local laboratory will report results to the center as early as possible in order to allow the Investigator to review the results no later than 24 hours after blood samples being taken.

Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled safety lab tests may be obtained at any time during the study to assess any perceived safety concerns.

9.3.2 Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at Day 1 and Day 8 ± 1. Approximately 30 mL will be collected for testing. Results will be obtained prior to dosing. A female subject will be considered of non-childbearing potential if they satisfy at least one of the following criteria:

1. 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;

2. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

3. Have medically confirmed ovarian failure.

All other female subjects will be considered to be of childbearing potential.

The investigator and site personnel will remind subjects at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant (e.g. had unprotected intercourse since the last visit).

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). 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.

9.3.3 Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

A general physical examination will be performed at Day 1 (randomization visit) and upon study termination (Day 8 ± 1 - final visit), as well as when judged necessary by the investigator. Examination will include: general condition, dermatologic, eyes, ears, nose, throat, neck, thyroid, heart, respiratory system, abdomen, kidneys, skeletal system, extremities, lymphatic system, CNS, neurological conditions according to the state of the art.

Any untoward findings identified on physical exams conducted after the administration of the first dose of investigational product will be captured as an adverse event, if those findings meet the definition of an adverse event.

9.3.4 Height and Weight

Height in cm and body weight in kilograms (kg) to the nearest 0.1 kg will be measured at Visits 1 and 4 (height at Visit 1 only).

For measuring weight, a scale with appropriate range and resolution should be 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.

9.3.5 Vital Signs (Blood Pressure and Pulse Rate)

Vital signs (including systolic blood pressure, diastolic blood pressure and pulse rate) will be measured at Visits 1 and 4:

- Blood pressure: Measurement after at least 5 minutes at rest in sitting position.

- Pulse rate: Measured after at least 5 minutes at rest in the sitting position.

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.

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.

9.4 Blood Volume

The total blood sampling volume for each subject in this study is approximately 20 mL (approximately 10 mL x 2). 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 9-2 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening (Visit 1)	Study Period (Visit 4)	Follow-Up	
Safety Labs	<10	1	1		<20
TOTAL					<20

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

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product or investigational assessment, whether or not considered related to the study product, including any washout or lead-in product or investigational assessment.

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 product including any washout or lead-in product or investigational assessment.

Events Meeting the AE Definition:

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

However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

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

10.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. 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 subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. 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 (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption

- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

All AEs, and therefore all SAEs will be collected immediately after a subject consents to participate in the study by the completion (signature) of the ICF and until 28 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

10.4 Reporting Procedures

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

The investigator (or medically qualified designee) 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 a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

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

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

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

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

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

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

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

It is essential to enter the following information:

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

The following are desirable and are of particular relevance for investigator and 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 in relation to the study product
- Outcome if known

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

CRO will then email the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSK CH (PPD), with copy to the appropriate GSK CH Study Manager as soon as possible, **but not later than 24 hours** 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.

The Investigator should also report to China health authorities and the Independent Ethics Committee (IEC) within 24 hours in written documentation with the report signed and dated.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

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

10.5.2 Assessment of Causality

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

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

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

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

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

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

10.6 Follow-up of 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 (serious and non-serious) will be followed until resolution, or until the condition stabilizes, or 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 CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

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

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH 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 (PPD).

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

10.7 Withdrawal Due to an Adverse Event

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

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

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

GSK CH 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 CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH 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 e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until at least 21 days after last administration of study product.

10.8.2 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 CRO 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 CRO. 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.

CRO will scan and email the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK CH (PPD) with copy to the appropriate GSK CH Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

11 DATA MANAGEMENT

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

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

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

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, 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 8 and 9. 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 Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

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

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

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

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 as applicable at the completion of the study.

11.2 Data Handling

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

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

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

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will

raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

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

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

11.3 Processing Subject Reported Outcomes

Paper based subject reported outcome (PRO) data may be collected from a diary, questionnaire, or other specified document, etc. and entered into the data management system (DMS).

All PRO source data should be reviewed by the study staff and the study monitor in order to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. Site staff cannot make any changes to subject diaries. If a subject makes a change to the subject diary, they must initial and date the change. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or GSK CH as required.

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO that will be forwarded to GSK CH or Third-Party Vendor.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Approximately 300 subjects will be randomized to ensure at least 240 evaluable subjects complete the study for the PP analysis population. A maximum of 40 randomized subjects per center will be allowed.

Approximately 120 subjects per treatment arm has been determined to provide 80% power to demonstrate non-inferiority of DDEA 2.32% gel b.i.d with DDEA 1.16% gel q.i.d. by comparing the two-sided 95% CI of the difference in mean change from baseline of VAS POM score between the two products with the non-inferiority margin of 13 mm. This assumes a treatment standard deviation of 22mm and allows for a possible small true treatment difference of 5mm in favor of DDEA 1.16%.

The margin of 13 mm (on a 100 mm VAS scale) was chosen as the literature reported minimally important clinical difference for an acute musculoskeletal injury (Todd et al 1995), with treatment differences smaller than 13mm considered as not clinically important. The standard deviation was obtained from a previous placebo-controlled ankle sprain study VOPO-P-307 with DDEA 2.32% gel.

12.2 Statistical Methods and Analytical Plan

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

12.2.1 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 modified intent-to-treat (mITT) population will consist of all randomized subjects who have at least one post baseline POM VAS assessment

The PP population includes all subjects from the mITT population who do not have any major protocol deviations that could confound the interpretation of the efficacy analyses. Protocol deviations that would exclude subjects from the PP population are defined in Section 12.2.2.

Before the study is unblinded, each actual post-baseline visit will be mapped to the target visit date to which it is chronologically closest. This corresponds to the following visit windows: Visit 2 (Days 2–4), Visit 3 (Days 4–6), Visit 4 (Days 7+). The numbering of the actual visits (from Visit 1 to Visit 4) will then be changed as needed to improve the correspondence of the actual visit dates to the protocol-specified schedule of visits, particularly in relation to Visit 3 (primary). Final determinations will also be made and documented before the study is unblinded to address visits that occur on Day 4 (which maps to two visit windows) or visits occurring well beyond the target date for the final visit or any other irregularities. Further detail is provided in the statistical analysis plan.

12.2.2 Exclusion of Data from Analysis

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

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

- Subjects failing to meet inclusion and exclusion criteria but were included in the study.
- Subjects without a Day 5 pain on movement VAS assessment
- Subjects with poor or moderate compliance with study treatment
- Subjects taking prohibited medication
- Subjects identified with other major protocol deviations

Further detail is provided in the statistical analysis plan.

12.2.3 Demographic and Baseline Characteristics

Demographic data, including age, gender and race, and other baseline data will be presented using descriptive statistics.

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.

12.2.4 Study Drug/Product Compliance and Use of Other Therapies

12.2.4.1 Study Drug/Product Compliance

Compliance is defined in terms of the total weight of study medication used and total number of applications made as follows:

• Good: > 80% of the gel has been applied and > 80% of scheduled applications made,

• Moderate: not Good and not Poor

• Poor: < 50% of the gel has been applied or < 50% of scheduled applications made.

The % of gel used will be computed relative to the actual number of applications made from randomization through the final visit multiplied by 2 g. This value is to be recorded in the CRF. Scheduled applications will include all scheduled applications through the day before the final visit. On day 1, the percentage of gel used will be calculated based on the possible number of administrations on that day. If only 3 were possible, then 100 % compliance on that day will be considered 3 applications.

Compliance will be summarized descriptively as (1) % of scheduled applications made, (2) % of gel used relative to number of actual applications * 2g, and (3) compliance category (Good/Moderate/Poor). Exposure to study drug will be summarized descriptively as (1) number of applications made and (2) total amount of gel used.

For subjects applying active gel only twice per day (DDEA 2.32%), and additional compliance and exposure computation will be performed relative to the tubes and applications of active gel.

12.2.4.2 Prior and Concomitant Medications

Prior and concomitant 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.

12.2.5 Primary Analysis(es)

The primary efficacy endpoint will be change from baseline in POM on Day 5 of treatment as assessed by a 100 mm VAS scale.

The following primary non-inferiority hypothesis will be tested for DDEA 2.32% vs DDEA 1.16%:

The null hypothesis is Diclofenac 2.32% DDEA Gel administered BID is inferior to Diclofenac 1.16% DDEA gel administered QID with the alternative hypothesis being Diclofenac 2.32% DDEA Gel administered BID is non-inferior to Diclofenac 1.16% DDEA gel administered QID.

Diclofenac 2.32% DDEA Gel administered BID will be declared non-inferior to Diclofenac 1.16% DDEA gel administered QID if the upper limit of the two-sided 95% confidence interval of the difference between their mean changes from baseline VAS POM responses is less than the established margin of 13 mm.

The primary analysis will be based on an analysis of covariance (ANCOVA) with treatment and center as factors and baseline value as a covariate to estimate the treatment difference two-sided 95% confidence interval for the primary endpoint to assess non-inferiority, using the per protocol and mITT analysis populations.

Evidence of a treatment-by-center interaction will be assessed by adding a factor for this interaction in a separate additional analysis model of the primary endpoint. If there is evidence of an interaction ($p<0.05$), then the primary endpoint outcome will also be summarized by center for further investigation and assessment

12.2.6 Secondary Analysis(es)

Secondary outcome measures (endpoints) include:

- Change from baseline of POM on VAS on Days 3 and 8 respectively
- Tenderness measured by pressure algometry on Days 3, 5 and 8 (change from baseline and difference between the measurement in injured area and contralateral area)
- Change from baseline Ankle Joint Function (Karlsson Scoring Scale) on Days 3, 5 and 8
- Circumference measurement of swelling (change from baseline in circumference of affected ankle and comparison to non- affected ankle by Figure of Eight method on Days 3, 5 and 8)
- Pain Intensity and Pain Relief
    - Sum of Pain Intensity Difference (SPID) – From hours 0 – 24 post first dose (corresponding to Day 1) and from hours 96 – 120 post first dose (corresponding to Day 5)
    - Total Pain Relief (TOTPAR)– From hours 0 – 24 post first dose (corresponding to Day 1) and from hours 96 – 120 post first dose (corresponding to Day 5)

TOTPAR and SPID will be calculated as weighted sums of the Pain Relief Score and Pain Intensity Difference at each timepoint respectively:

$TOTPAR = \Sigma R_t^x (time_t – time_{t-1})$

Where R_t = the pain relief score at time $_t$ and $time_t$ = time in hours post first dose

$SPID_t = \Sigma PID_t (time_t – time_{t-1})(h)$

Where PI is pain intensity

- Use of rescue medication, for ankle sprain and overall
    - Total number of tablets used
    - Total number of days on which rescue medication was used

Figures will show the time course of outcomes by treatment group for key quantitative outcomes.

For POM, Karlsson score, tenderness, swelling and diary assessments (SPID and TOTPAR), an ANCOVA model including treatment group and center as main effects, and the baseline value as covariate (those outcomes for which there is a baseline) will be used for analysis, with the treatment difference and 95% confidence interval (two-sided) presented for each assessment.

Use of rescue medication (number of tablets and days used) will be compared between treatments using the CHM method (modridit scores) stratified by center, with the median treatment differences and 95% confidence intervals (2-sided) presented using Hodges-Lehmann estimation.

These secondary endpoints will be analyzed using the per protocol and mITT populations.

12.2.7 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 Visit 1 and at Visit 4 will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group. Shift tables (between Visit 1 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 4 and changes in vital signs from Visit 1 (baseline) to Visit 4 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.

12.2.8 Other Analysis(es)

Not applicable.

12.2.9 Handling of Dropouts and Missing Data

Multiple imputation using a simulation-based statistical technique for handling missing data as proposed by [Rubin, 1987] will be used. Multiple imputation will consist of three steps:

1. Imputation step. Missing values will be identified and replaced by a random sample of plausible values imputations (completed datasets). Under assumption of monotone missingness an imputation model with regression baseline parameters will be applied. Five imputed datasets have traditionally been suggested to be sufficient on theoretical grounds, but 50 datasets seem preferable and will be used to reduce sampling variability from the imputation process.

2. Completed-data analysis (estimation) step. The desired analysis will be performed separately for each dataset generated during the imputation step, following the ANCOVA method described in section 12.2.5.

3. Pooling step. The results obtained from each completed-data analysis will be combined into a single multiple-imputation result.

A sensitivity analysis will also be performed with no imputations for missing data and using a repeated measure mixed effect model with subject as random, and with center, treatment and timepoint (Day 3, 5 and 8) as factors and baseline value as a covariate. The treatment differences and two-sided 95% CIs for the primary end-point will be estimated for the PP and mITT analysis populations.

No imputation is planned for missing diary card pain intensity and relief assessments.

12.2.10 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH 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 CH 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 CH 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.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH 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.

13.3 Regulatory and Ethical Considerations

13.3.1 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.

13.3.2 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), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016)**,** guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

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

13.3.3 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/CRO 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.

13.3.4 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.

13.3.5 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.

13.4 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 CH processes.

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

13.5 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 CH site or other mutually-agreeable location.

GSK CH 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 CH Policy.

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

13.6 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 CH 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 15 years from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH 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 CH 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.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of DDEA 2.32% at any time. 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.

14 REFERENCES

1. [Study VOPO-P-307] Clinical Study report. A randomized, double-blind, multi-center, placebo controlled, 3-treatment arm, parallel group study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice or three times daily in patients with acute ankle sprain, dated 04 May 2010
2. [Study VOPO-PE-102] Clinical Study report. A randomized, 4-period, crossover study on the systemic exposure to diclofenac in healthy volunteers after treatment with topical diclofenac diethylamine 2.32% gel under non-occlusive and semi-occlusive conditions, topical diclofenac diethylamine 1.16% gel, and oral diclofenac sodium 50 mg tablets, dated 23 Oct 2003
3. PPD
4. [Study NF113] Clinical Study report. A multicenter, parallel group, randomized, double-blind, placebo-controlled study investigating efficacy of Voltaren Emulgel 1.16% gel compared with placebo gel in patients with soft tissue trauma
5. PPD
6. Chesterton LS, Barlas P, Foster NE et al. (2003) Gender differences in pressure pain threshold in healthy humans. Pain; 101: 259-266
7. Fischer AA (1987) Pressure algometry over normal muscles: Standard values, validity and reproducibility of pressure threshold. Pain; 30(1): 115-126
8. Fong DT, Hong Y, Chan LK et al. (2007) A systematic review on ankle injury and ankle sprain in sports. Sports Med; 37: 73-94
9. Friends J, Augustine E, Danoff J (2008) A comparison of different assessment techniques for measuring foot and ankle volume in healthy adults. J Am Podiatr Med Assoc; 98: 85-94.
10. Galer BS, Rowbotham M, Perander J et al. (2000) Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. J Pain Symptom Manage; 19: 287-294
11. Gan TJ. (2010) Diclofenac: an update on its mechanism of action and safety profile. Curr Med Res Opin; 26:1715-1731
12. ICH Topic E6 (R2) Guideline for Good Clinical Practice, Nov 2016
13. Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28.
14. Heyneman C, Lawless-Liday C, and Wall GC (2000) Oral versus topical NSAIDs in rheumatic diseases. A comparison. Drugs; 60: 555-574
15. Karlsson J, Petersen L (1991) Evaluation of ankle joint function: the use of a scoring scale. The Foot 1; 1: 15-16
16. Karlsson J, Eriksson B, Swand L (1996) Early functional treatment for acute ligament injuries of the ankle joint. Scand J Med Sci Sports; 6: 341-345
17. Mason L, Moore RA, Edwards JE, et al. (2004) Topical NSAIDs for acute pain: a metaanalysis. BMC Fam Pract; 5: 10.

18. Niethard FU, Gold MS, Solomon GS et al. (2005) Efficacy of diclofenac diethylamine gel in osteoarthritis of the knee. J Rheumatol; 32:2384 – 92.
19. Nussbaum EL, Downes L. (1998) Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. Phys Ther; 78: 160-169.
20. Ohrbach R, Gale EN (1989) Pressure pain threshold in normal muscles: reliability, measurement effects, and topographic differences. Pain; 37: 257-263
21. Petersen EJ, Irish SM, Lyons CL et al. (1999) Reliability of water volumetry and the figure of eight method on patients with ankle joint swelling. J Orthop Sports Phys Ther; 29: 609-915.
22. Predel HG, Hamelsky S, Gold M, et al. (2012) Efficacy and safety of diclofenac diethylamine 2.32% gel in acute ankle sprain. Med Sci Sports Exer; 44:1629-36.
23. Predel HG, Koll R, Pabst H et al. (2004) Diclofenac patch for topical treatment of acute impact injuries: a randomised, double-blind, placebo-controlled, multicentre study. Br J Sports med; 38: 318-323
24. Rademacher J, Jentsch D, Scholl M A (1991) Diclofenac concentrations, in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease. Br J Clin Pharm; 31: 537-541.
25. Rainsford KD, Kean WF, Ehrlich GE (2008) Review of the pharmaceutical properties and clinical effects of the topical NSAID formulation, diclofenac epolamine. Curr Med Res Opin; 24: 2967-2992.
26. Rimando MP (2008) Ankle sprains. eMedicine, Physical Medicine and Rehabilitation, Lower Limb Musculoskeletal Conditions
27. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons, Inc 1987.
28. Stöckle U, Hoffmann R, Schütz M et al. (1997) Fastest reduction of posttraumatic edema: continous cryotherapy or intermittent impulse compression? Foot Ankle Int; 18: 432-438.
29. Tatro Adams D, Mcgann SF, Carbone W (1995) Reliability of the figure-of eight method of ankle measurement. J Orthop Sports Phys Ther; 22: 161-163
30. Todd KH, Funk KG, Funk JP, et al. (1996) Clinical significance of reported changes in pain severity. Ann Emerg Med; 27:485-9.
31. Vaile JH, Davis P (1998) Topical NSAIDs for musculoskeletal conditions. A review of the literature. Drugs; 56: 783-799.
32. Wetzel D, Menke W, Dieter R et al. (2002) Escin/diethylammonium salicylate/heparin combination gels for the topical treatment of acute impact injuries: a randomised, double blind, placebo controlled, multicentre study. Br J Sports Med; 36: 183-188
33. Wolfe M, Uhl T, Mattacola C, McCluskey L. (2001) Management of ankle sprains. American Family Physician; 63: 93-104
34. World Medical Association Declaration of Helsinki, 64th General Assembly, Fortaleza 2013.
35. Zacher J, Altman R, Bellamy N et al. (2008) Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin; 24: 925-950.

15 APPENDIX

15.1 ABBREVIATIONS

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

Table 15-1 Abbreviation

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BA	bioavailability
BE	bioequivalence
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
C_{av}	average concentration
CDS	core data sheet
C_{eff}	efficacious concentration
CI	confidence interval
CL/F	apparent oral clearance
CL_r	renal clearance
C_{max}	peak or maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CSA	clinical study agreement
CSF	cerebrospinal fluid
CTA	clinical trial application
DCT	data collection tool
DDEA	diclofenac diethylamine
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FRP	Females of Reproduction Potential
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HDL-C	high density lipoprotein cholesterol

Abbreviation	Term
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IUS	Intrauterine system
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LSLV	last subject last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
mITT	modified intention to treat
MTD	maximum tolerated dose
N/A	not applicable
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAID	non-steroidal anti inflammatory drug
PD	pharmacodynamics
PG	pharmacogenomics
PI	principal investigator
PK	pharmacokinetics
POM	pain on movement
PP	per protocol
PR	pulse rate
PT	prothrombin time
QC	quality control
QTc	corrected QT
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	summary of product characteristics
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement

Abbreviation	Term
$T_{1/2}$	terminal half-life
THC	tetrahydrocannabinol
T_{max}	time to reach maximum concentration
ULN	upper limit of normal
US	United States
USPI	United States package insert
VAS	visual analogue scale
V_z/F	apparent oral volume of distribution
WBC	white blood cell