TITLE PAGE

PROTOCOL NUMBER	**:**	MYL-1601N-3002
CLINICAL PHASE	**:**	Bioequivalence study with clinical endpoint
PROTOCOL TITLE	**:**	A Randomized, Double blind, Three-arm, Parallel, Placebo-controlled, Clinical Study to Evaluate the Bioequivalence using Clinical Endpoint of Diclofenac Sodium Gel, 1% (Mylan Inc.) to Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis Consumer Health, Inc.) in Patients with Osteoarthritis (OA) of the Knee
PROTOCOL VERSION	**:**	1.0
DATE	**:**	06 Dec 2016
SUPERSEDED VERSION AND DATE	**:**	None

SPONSOR:

Mylan [redacted],

[redacted]

CONTRACT RESEARCH ORGANIZATION**:**

[redacted]

"All financial and nonfinancial support for this study will be provided by Mylan. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Mylan. The study will be conducted according to the International Conference on Harmonisation harmonized tripartite guideline E6 (R1): Good Clinical Practice."

Protocol Approval- Sponsor Signatory

STUDY TITLE: A Randomized, Double blind, Three-arm, Parallel, Placebo-controlled, Clinical Study to Evaluate the Bioequivalence using Clinical Endpoint of Diclofenac Sodium Gel, 1% (Mylan Inc.) to Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis Consumer Health, Inc.) in Patients with Osteoarthritis (OA) of the Knee.

PROTOCOL VERSION: 1.0 **PROTOCOL DATE: 06 DEC 2016**

Protocol accepted and approved by:

[redacted]

Signature **Date**

Clinical Safety –

[redacted]

Signature **Date**

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PROTOCOL VERSION: 1.0 **PROTOCOL DATE: 06 DEC 2016**

Protocol accepted and approved by:

Overall Approval of the protocol –

[redacted]

Signature **Date**

Clinical Safety –

[redacted]

6th DEC 2016

Signature **Date**

Biostatistics–

[redacted]

9th December 2016

Signature **Date**

Regulatory –

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Signature **Date**

Biostatistics–

[redacted]

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Regulatory –

[redacted]

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Sponsor Representative / Authorized Signatory Contact Details:
Project Manager Contact Details:
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LIST OF ABBREVIATIONS

ACE	:	Angiotensin-converting-enzyme
ACR	:	American College of Rheumatology
AE	:	Adverse Event
ANCOVA	:	Analysis of Covariance
BUN	:	Blood Urea Nitrogen
CABG	:	Coronary Artery Bypass Graft
CFR	:	Code of Federal Regulations
CI	:	Confidence Interval
CMC	:	Carpometacarpal
COX	:	Cyclooxygenase
CRA	:	Clinical Research Associate
CRO	:	Contract Research Organization
DCF	:	Data Clarification Form
EC	:	Ethics Committee
ECG	:	Electrocardiogram
eCRF	:	Electronic – Case Report Form
FDA	:	Food and Drug Administration
GCP	:	Good Clinical Practice
JSN	:	Joint Space Narrowing
gm	:	Grams
GMP	:	Good Manufacturing Practice
HBSag	:	Hepatitis B Surface Antigen

HCV	:	Hepatitis C virus
HIV	:	Human Immunodeficiency Virus
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Institutional Ethics Committee
IMP	:	Investigational Medicinal Products
IRB	:	Institutional Review Board
ITT	:	Intent to Treat
IUD	:	Intrauterine Device
IW	:	Impartial Witness
LAR	:	Legally Acceptable Representative
LOCF	:	Last Observation Carried Forward
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	Milligram
mITT	:	Modified Intent to Treat
mm	:	Millimeter
NIMP	:	Non-investigational medicinal products
NSAIDs	:	Non-Steroidal Anti-Inflammatory Drugs
OA	:	Osteoarthritis
OTC	:	Over the counter
PG	:	Prostaglandins

POM	:	Pain on Movement
PP	:	Per Protocol
PSRM	:	Product Safety and Risk Management
RLD	:	Reference Listed Drug
SAE	:	Serious Adverse Event
SAF	:	Safety Population
SAS	:	Statistical Analysis System
SUSAR	:	Suspected Unexpected Serious Adverse Reaction
ULN	:	Upper Limit Normal
USFDA	:	United States Food and Drug Administration
USP	:	United States Pharmacopoeia
VAS	:	Visual Analog Scale
WOMAC	:	Western Ontario and McMaster Universities Osteoarthritis Index

FACILITIES

Contract Research Organization

[redacted]

Clinical Laboratory Services

[redacted]

Data Management and Statistical Services

Sponsor's designated facility

1. SYNOPSIS

Protocol No:	MYL-1601N-3002
Title of Study:	A Randomized, Double blind, Three-arm, Parallel, Placebo-controlled, Clinical Study to Evaluate the Bioequivalence using Clinical Endpoint of Diclofenac Sodium Gel, 1% (Mylan Inc.) versus Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% (Novartis Consumer Health, Inc.) in Patients with Osteoarthritis (OA) of the Knee.
Short Title:	Bioequivalence study with clinical endpoint of generic diclofenac gel with Voltaren® gel in patients with osteoarthritis of knee.
Study Phase:	Bioequivalence study with clinical endpoint
Sponsor:	Mylan [redacted]
Objectives:	*Primary Objectives:* 1. To determine the clinical equivalence of Test Drug (Diclofenac sodium gel of 1% of Mylan Inc.) with the Reference Listed Drug (RLD) (Voltaren® Gel 1% of Novartis Consumer Health, Inc.) as measured by mean change from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert (version 3.1) pain score. 2. To establish superiority of the Test Drug and Reference Listed Drug (RLD) over placebo in mean change from baseline in the WOMAC Likert (version 3.1) pain score. *Secondary Objectives:* 1. To assess the safety and tolerability of study treatments. 2. To determine the clinical equivalence of Test Drug(Diclofenac Sodium gel) with the Reference Listed Drug (RLD) (Voltaren® Gel) as measured by mean change from baseline in subjects whose baseline WOMAC Likert (version 3.1) pain scores are less than or equal to 10.
Design	Randomized, Double-blind, Multicentric, Parallel, Active and Placebo Controlled, Three Arm, Bioequivalence study with clinical endpoint in the ratio of 1:1:1 of Test drug, Reference drug and Placebo respectively
Test Product	Diclofenac Sodium Gel, 1% manufactured by Mylan Inc.
Reference Product	Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% manufactured by Novartis Pharma Produktions GmbH, marketed by: Endo Pharmaceuticals Inc., Malvern, PA

	19355
Placebo	Placebo (vehicle) gel manufactured by Mylan Inc.
Non-Investigational Medicinal Products (NIMP)	Acetaminophen (paracetamol) tablet will be given as a rescue medication
Study Rationale	Mylan is developing a generic diclofenac sodium gel to the Reference Listed Drug (RLD) Voltaren® gel. This randomized, double-blind, three-arm, placebo controlled, bioequivalence study with clinical endpoint has been designed to establish clinical equivalence and safety of Mylan's diclofenac gel in the symptomatic treatment of osteoarthritis of knee compared to Voltaren® gel and to establish superiority in efficacy of both compared to a placebo (vehicle) gel. The planned study design is also in compliance with the United States Food and Drug Administration's Draft Guidance for Diclofenac Sodium Topical Gel.[1]
Dose and Mode of Administration	All subjects will have to apply 4 gm of gel to the affected area of target knee 4 times daily. At the start of run-in period, placebo gel will be provided to the qualified subjects for application and during the treatment period, Mylan's Diclofenac Sodium Topical Gel 1%, Voltaren® Gel 1% (Reference Listed Drug), or Placebo gel will be provided to the subjects for application. The proper amount of gel will be measured using the dosing card. The gel will be applied within the rectangular area of the dosing card up to 4-gram line. Subjects will be instructed to rinse and dry the dosing card after use. Subjects will be trained via a detailed and translated instruction subject diary on how to administer the study drug.
Study Population	Male or non-pregnant female aged ≥ 35 years with a clinical diagnosis of osteoarthritis of the knee according to the American College of Rheumatology (ACR) criteria
Number of Subjects	Around 1212 patients will be randomized in this study (404 patients in each treatment arm).
Study Period	Total study duration for the clinical part will be around 56 days that includes screening period of 28 days (including run-in period of 7 (+ 4) days) and treatment period of 4 weeks.
Inclusion Criteria:	1. Healthy male or non-pregnant female aged ≥ 35 years with a clinical diagnosis of OA of the knee according to the American College of Rheumatology (ACR) criteria[2] i.e. Knee pain along with at least 3 of the following 6 criteria a. Age > 50 years

	b. Stiffness < 30 minutes c. Presence of crepitus d. Bony tenderness e. Bony enlargement f. No palpable warmth 2. Symptoms in target knee for at least 6 months prior to screening 3. Knee (not referred) pain in target knee for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.) 4. Pain in the target knee requiring the use of NSAIDs or acetaminophen (paracetamol) (topical or oral treatments). 5. Subject having an X-ray of the target knee, taken no more than 1 year before baseline, showing evidence of OA with Kellgren-Lawrence grade 1-3 disease. 6. After discontinuing all pain medications(placebo run – in period) for at least 7 days, has at least moderate pain on movement (POM) for target knee, defined as a baseline score of ≥ 50 mm on a 0-100 mm Visual Analog Scale (VAS) immediately prior to randomization. 7. After discontinuing all pain medications (placebo run – in period) for at least 7 days has a baseline Western and Ontario McMaster Universities Osteoarthritis Index (WOMAC Likert (version 3.1)) pain subscale of ≥ 9 immediately prior to randomization. 8. Able to tolerate rescue medication with only acetaminophen (paracetamol) taken as l-2 tablets up to a maximum of 2 gm per day for the duration of the study. 9. Subjects who can read and understand WOMAC pain sub scale. 10. If female, patient must be either postmenopausal for at least one year prior to randomization, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or practicing the following methods of birth control: a) Oral Contraceptives or Intrauterine Device in place for at least 3 months prior to the start of the study and remaining in place during the study period, or b) Double Barrier methods containing or used in conjunction with a spermicidal agent, or c) Contraceptive Patches/ Implants, or d) Abstinence: Subjects who will be practicing abstinence will agree to have a documented second acceptable method of birth control if the subject become sexually active during the course of her study participation.

Exclusion Criteria:	1. Pregnant or lactating or planning to become pregnant during the study period. 2. X-ray showing evidence of OA with Kellgren-Lawrence grade 4 disease. 3. History of OA pain in the contralateral knee requiring medication (OTC or prescription) within 1 year prior to screening. 4. After discontinuing all pain medications (placebo run-in period)for at least 7 days, had a baseline score of ≥ 20 mm on a 0-100 mm Visual Analog Scale (VAS) for the contralateral knee immediately prior to randomization. 5. History of OA of either Hip or Hands. 6. History of secondary OA (e.g. congenital, traumatic, gouty arthritis) or rheumatoid arthritis. 7. History of chronic inflammatory disease (e.g., colitis) or fibromyalgia. 8. History of drugs or alcohol abuse with in the previous year. 9. Symptomatic peripheral vascular disease of the study leg (prior or current). 10. Any musculoskeletal condition that would impede measurement of efficacy at the target knee. 11. History of regular headaches or backache which warrants frequent use of acetaminophen (paracetamol) or NSAIDs within the previous year. 12. Concomitant skin disease at the application site which may affect study drug application or tolerability evaluation. 13. History of active asthma within the previous year that may require periodic treatment with systemic steroids during the study period (note: inhaled steroids for this condition are allowed). 14. History of aspirin sensitive asthma. 15. History of uncontrolled hypertension (blood pressure more than 150/100 mm of Hg) in spite of treatment with in the previous year. 16. History of myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function (Serum creatinine > 1.5 x ULN), or liver disease with in the previous year. 17. History of coronary artery bypass graft within 6 months of screening. 18. History of gastrointestinal bleeding or peptic ulcer disease in last one year. 19. Known allergy to aspirin, nonsteroidal anti-inflammatory drugs (NSAID) or acetaminophen (paracetamol). 20. Elevated transaminases (≥ 3 times ULN) and hemoglobin < 9.0 g/dL at screening. 21. Viscosupplementation in any joint including the target knee within 6 months prior to screening. 22. Receiving physical therapy (at an outpatient/clinic setting) for the lower extremities or having received physical therapy for the lower extremities within 1 month before screening.

	23. Use of anticoagulants, ACE-inhibitors, cyclosporine, diuretics, lithium, or methotrexate prior to 30 days of screening. 24. Concomitant use of intra articular corticosteroids, systemic corticosteroids, topical corticosteroids, or immunosuppressive drugs or their use prior to 30 days of screening. 25. Concomitant acetylsalicylic acid therapy other than a stable low dose used for cardiac prophylaxis (maximum 162 mg daily)[3] taken for at least 3 months prior to enrollment and maintained throughout the duration of the study. 26. History of major surgery or previous damage to the study knee at any time, or minor knee surgery (e.g. any surgery other than major surgery including, but not limited to, cartilage repair, collateral ligament repair, or arthroscopic debridement) to the study knee within 1 year prior to screening. 27. Known history of positive HIV, HCV or HBsAg. 28. Tense effusion requiring aspiration. 29. Subjects who have been treated with an investigational drug or investigational device within a period of 30 days prior to enrollment. 30. Any other acute or chronic illness that could compromise the integrity of study data or place the subject at risk by participating in the study.
Study Design& Methodology:	This is a double-blind, multiple-site, randomized, parallel-design study to investigate the clinical endpoint bioequivalence of Mylan's Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel, 1% (Novartis Consumer Health, Inc.) and to investigate that both the active products are superior to placebo. Subjects will have to visit the clinic for the following visits during the study – Visit 1 – Screening visit (within 28 days prior to randomization) Visit 2 – Start of Placebo Run-in period (Day -11 to Day -7) Visit 3 – Randomization (baseline) visit (Day 0) Visit 4 – Interim visit (Week 2/Day 14 ± 4) Visit 5 – End of study (Week 4/Day 28 ±4)/ Early termination visit After informed consent process and completion of all screening assessments, the eligible subjects will be requested to stop the currently ongoing osteoarthritis drug therapy. The wash out period (run-in period) of 7 days or ≥ 5 half-life of previous osteoarthritis drug therapy, whichever is longer, will be maintained before the baseline visit. Subjects will undergo at least 7 days of placebo run-in period. In case subject extends run-in period beyond 11 days, continuation of the subject will be decided in consultation with medical monitor. The Pain on Movement (POM) score on a Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Likert scale version 3.1) pain score will be recorded at the start of run-in period and at the end

	of run-in period (i.e. immediately prior to randomization on the day of baseline visit). Recording of the VAS will be done for both the knees and recording of the WOMAC pain score will be done for the target knee. During the washout period, subjects will undergo a single-blind placebo run-in period. Subjects will be provided with placebo gel for the administration. Approximately 4 gm dose of placebo gel will be applied to the target knee four times daily for at least 7 days. Target knee means the knee, which is more painful, will be identified during the screening visit. First administration of gel will be supervised at the study center, with subsequent applications self-administered on an outpatient basis. At baseline visit, subjects will be randomly assigned in 1:1:1 fashion to Mylan's Diclofenac Sodium Topical Gel 1%, Voltaren® Gel 1% (Reference Listed Drug), and Placebo. All the subjects will be instructed to apply the gel next day (Day 1) onwards. All subjects will be applying approximately 4 gm dose of either Mylan's Diclofenac Sodium Topical Gel 1% or Voltaren® Gel 1% (Reference Listed Drug) or Placebo gel to the arthritic target knee four times daily for 4 weeks. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Likert version 3.1) pain score for the target knee and pain on movement (POM) on a Visual Analog Scale (VAS) for both the knee will be recorded on Week 2 and Week 4 from the start of the treatment. Acetaminophen (paracetamol) tablets will be given to the subjects for use as a rescue medication or for the treatment of aches and pains unrelated to knee pain such as headache during treatment period (except 3 days prior to Visit 4 and Visit 5) Maximum allowed dose of acetaminophen (paracetamol) will be 2 gm/day. Consumption of rescue medications in terms of number of tablets consumed will be monitored. Subject diary will be provided to subjects to record study medication gel application, rescue medication, side effects, and concomitant medication details. Subjects will be trained regarding how to use the subject diary. Subject diary will be used to evaluate drug application compliance. Subjects will be trained via a detailed and translated instruction subject diary on how to administer the study drug. Physical examination will be done during each visit (except at the start of run-in

	period visit). Application site reaction assessment will be done on each visit after start of run-in period. A standard 12-lead ECG will be recorded after 5 minutes of rest in the supine position on screening visit and on end of study visit. Vital signs will be measured after 5 minutes of rest (sitting) on each visit. Serum pregnancy test for females of childbearing potential will be performed at screening and end of treatment visit. The urine pregnancy test can be performed if clinically indicated during other visits. If urine pregnancy is found to be positive, serum pregnancy test will be done for confirmation. If serum pregnancy test will found positive then patient will be excluded from the study and followed up. Laboratory assessments like hematology and biochemistry will be performed during screening and end of study. The hematology and biochemistry at screening to be performed within 14 days prior to baseline visit. If the gap between lab assessments and baseline visit will be more than 14 days, the lab assessments will be repeated at baseline visit. Laboratory investigations (if clinically significant) can be repeated once as per investigator's discretion. *Telephone contact:* Principal investigator or designee will contact the subjects approximately midway between the visit 3-4 and visit 4-5 for assessment of the well-being, adverse event, concomitant medication, and treatment compliance. Additional telephonic contact will be done to remind the subject regarding stoppage of rescue medication usage prior to scheduled visits (Visit 4, and Visit 5). The same will be documented in the source notes. Statistical comparisons will be made between test and reference, test and placebo, and reference and placebo.
Study Endpoints:	**Efficacy Endpoints:** Primary Efficacy Endpoint: • Mean change in the total WOMAC pain subscale score for the target knee, from baseline to week 4 Secondary Efficacy Endpoints: • Mean change in the total WOMAC pain subscale score for the target knee, from baseline to week 2. • Mean change in the WOMAC pain subscale score at week 4 for subgroup subjects whose baseline WOMAC pain score less than or equal to 10. • Mean change in pain on movement (POM) on a Visual Analog Scale (VAS) for target knee from baseline to week 4

	• Average number of days of acetaminophen (paracetamol)consumption during the trial • Average dose of acetaminophen (paracetamol)during the trial **Safety Endpoints:** • The incidence of treatment-emergent adverse events. • Local tolerability evaluation
Statistical Methods:	**Statistical Methods for Bioequivalence:** Bioequivalence will be established for the primary endpoint (WOMAC® Likert version 3.1) if the 90% confidence interval for the test/reference ratio of mean change from baseline to week 4 is contained within [0.80, 1.25], using the per-protocol population. The compound hypothesis to test is: H_0: $\mu T / \mu R \leq \theta_1$ or $\mu T / \mu R \geq \theta_2$ versus H_A : $\theta_1 < \mu T / \mu R < \theta_2$ Where μT = mean of test treatment, and μR = mean of reference treatment. H_0 will be rejected with a type I error $\alpha = 0.05$ (two 1-sided tests), if the 90% confidence interval for the ratio of means between test and reference products (μT / μR) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products. **Statistical Methods for Superiority:** As a parameter for determining adequate study sensitivity, the Test Drug and RLD should both be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint (mean change from baseline), using the mITT study population and last observation carried forward (LOCF). H_0: μT or μR ≥ μPlacebo versus H_A : μT or μR < μPlacebo Where μT = mean of test treatment, and μR = mean of reference treatment. H_0 will be rejected with a type I error $\alpha = 0.05$ (2-sided test). Rejection of the null hypothesis H_0 supports the conclusion of superiority to placebo. Analysis of covariance (ANCOVA) will be used to compare Test Drug to placebo and RLD to placebo separately. The model will consist of treatment, investigator and baseline value as covariate. **Analysis Populations:** The following 3 analysis populations will be used in the statistical analyses: • Per-protocol (PP) population: Includes all randomized subjects who meet all inclusion/exclusion criteria, compliant with the assigned study treatment, return to the study site for the primary endpoint visit within the specified window (± 4 days) OR discontinue from the study as a treatment failure, and do not have any protocol violations. • Modified Intent-to-treat (mITT) population: includes all randomized subjects

	who meet all inclusion/exclusion criteria, receive study treatment, and return for at least one post-baseline visit. • Safety (SAF) population: All randomized subjects who receive at least one study treatment. Note: Patients discontinuing early from the study due to lack of treatment effect will be included in the PP population, using Last Observation Carried Forward (LOCF). Subjects discontinuing early for other reasons will be excluded from the PP population, but will be included in the mITT population, using Last Observation Carried Forward (LOCF).
Ethical Issues	The study will commence only after a written approval is obtained from the Institutional Review Board for the submitted protocol, ICD and other relevant documents. The study will be conducted as per the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2006), ICH-GCP Guidelines and in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013).

2. INTRODUCTION AND STUDY RATIONALE

2.1. Overview of Study Indication

Osteoarthritis is a common degenerative disorder of the articular cartilage associated with hypertrophic changes in the bone. Risk factors include genetics, female sex, past trauma, advancing age, and obesity. The most common symptom of osteoarthritis is joint pain. The pain tends to worsen with activity, especially following a period of rest; this has been called the gelling phenomenon. Osteoarthritis can cause morning stiffness, but it usually lasts for less than 30 minutes, unlike rheumatoid arthritis, which causes stiffness for 45 minutes or more. Patients may report joint locking or joint instability. These symptoms result in loss of function, with patients limiting their activities of daily living because of pain and stiffness. The joints most commonly affected are the hands, knees, hips, and spine, but almost any joint can be involved. Osteoarthritis is often asymmetric. A patient may have severe, debilitating osteoarthritis of one knee with almost normal function of the opposite leg.[4] Osteoarthritis (OA) of the knee is a major cause of pain and locomotor disability worldwide.[5] In the United States, approximately 240 per 100,000 persons per year have knee osteoarthritis. In 2010, approximately 9.9 million adults had symptomatic knee osteoarthritis.[6]

2.2. Current Treatments for Study Indication

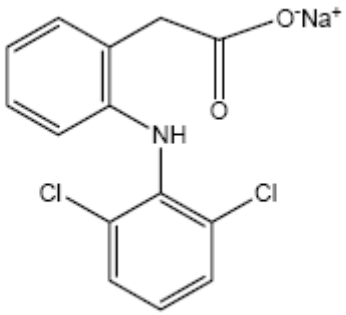
Pharmacologic modalities conditionally recommended for the initial management of patients with knee OA include acetaminophen (paracetamol), oral and topical NSAIDs, tramadol, and intra-articular corticosteroid injections. Intra-articular hyaluronate injections, duloxetine, and opioids are conditionally recommended in patients who had an inadequate response to initial therapy.[7]

Topical diclofenac significantly reduced pain and morning stiffness and improved physical function and patient global assessment without major adverse effects reported in patients with OA of the knee. It was reported that topical diclofenac sodium gel 1% is superior to placebo vehicle gel.[8,9,10]

2.3. Reference Product Information (Voltaren® Gel)

VOLTAREN® GEL (diclofenac sodium topical gel) is a nonsteroidal anti-inflammatory drug (NSAID) for topical use only. The chemical name is 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid, monosodium salt. The molecular weight is 318.14. Its molecular formula is $C_{14}H_{10}Cl_2NNaO_2$, and it has the following chemical structure.[11]

The structural formula of diclofenac is:



Clinical Pharmacology[11]

Mechanism of Action: Diclofenac has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of VOLTAREN® gel, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenases (COX-1 and COX-2).

Diclofenac is a potent inhibitor of prostaglandin synthesis *in-vitro*. Diclofenac concentrations reached during therapy have produced *in-vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Pharmacokinetics: The pharmacokinetics of VOLTAREN® GEL were assessed in healthy volunteers following repeated applications during 7 days of VOLTAREN® GEL to 1 knee (4 x 4 g per day) or to 2 knees and 2 hands (4 x 12 g per day) versus the recommended oral dose of diclofenac sodium for the treatment of osteoarthritis (3 x 50 mg per day). A summary of the pharmacokinetic parameters is presented in below table:

Table 1: Pharmacokinetic Parameters and Comparison of VOLTAREN® GEL to Oral Diclofenac Sodium Tablets after Repeated Administration

Treatment	**Cmax (ng/mL) Mean ± SD % of Oral (CI)**	**Tmax (hr) Median Range**	**AUC_{0-24} (ng.h/mL) Mean ± SD % of Oral (CI)**
VOLTAREN® GEL 4 x 4 g per day (=160 mg diclofenac sodium per day)	15 ± 7.3 0.6% (0.5-0.7)	14 (0-24)	233 ± 128 5.8% (5-6.7)
VOLTAREN® GEL 4 x 12 g per day (=480 mg diclofenac sodium per day)	53.8 ± 32 2.2% (1.9-2.6)	10 (0-24)	807 ± 478 19.7% (17-22.8)

Treatment	Cmax (ng/mL) Mean ± SD % of Oral (CI)	Tmax (hr) Median Range	AUC_{0-24} (ng.h/mL) Mean ± SD % of Oral (CI)
Diclofenac sodium tablets, orally 3 x 50 mg per day (=150 mg diclofenac sodium per day)	2270 ± 778 100%	6.5 (1-14)	3890 ± 1710 100%

Cmax = maximum plasma concentration, tmax=time of Cmax. AUC_{0-24}=area under the concentration time curve. SD=standard deviation. CI=confidence interval.

The pharmacokinetics of VOLTAREN® GEL has been tested under conditions of moderate heat (application of a heat patch for 15 minutes prior to gel application) and of moderate exercise (first gel application followed by a 20-minute treadmill exercise). No clinically relevant differences of systemic absorption and of tolerability were found between applications of VOLTAREN® GEL (4 x 4 g per day on 1 knee) with and under the conditions tested. However, the pharmacokinetics of VOLTAREN® GEL were not tested under the condition of heat application following gel application. Therefore, concurrent use of VOLTAREN® GEL and heat is not recommended.

2.4. Clinical Experience

Study 1 evaluated the efficacy of VOLTAREN® GEL for the treatment of osteoarthritis of the knee in a 12-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial. VOLTAREN® GEL was administered at a dose of 4 g, 4 times daily, on 1 knee (16 g per day). Pain as assessed by the patients at Week 12 using the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) Pain Sub index was lower in the VOLTAREN® GEL group than the placebo group.

Study 2 evaluated the efficacy of VOLTAREN® GEL for the treatment of osteoarthritis in subjects with osteoarthritis of the hand in an 8-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group study. VOLTAREN® GEL was administered at a dose of 2 g per hand, 4 times daily, on both hands (16 g per day). Pain in the target hand as assessed by the patients at Weeks 4 and 6 on a visual analogue scale from 0 to 100 was lower in the VOLTAREN® GEL group than the placebo group.[11]

Table 2: Efficacy outcomes of VOLTAREN® GEL in Studies 1 and 2

Efficacy outcomes of VOLTAREN® GEL in Studies 1 and 2				
		VOLTAREN® GEL	Placebo (Vehicle)	Adjusted Difference (Placebo - VOLTAREN® GEL)
Study 1 (Knee) WOMAC Pain * #	Sample Size	127	119	
	Mean Outcome	28	37	Δ = 7†
	95% Confidence			(1, 12)

Efficacy outcomes of VOLTAREN® GEL in Studies 1 and 2				
		VOLTAREN® GEL	Placebo (Vehicle)	Adjusted Difference (Placebo - VOLTAREN® GEL)
at Week 12	Interval			
Study 2 (Hand) Pain Intensity # at Week 4	Sample Size	198	187	
	Mean Outcome	43	50	Δ = 7 ‡
	95% Confidence Interval			(2, 12)
Study 2 (Hand) Pain Intensity # at Week 6	Sample Size	198	187	
	Mean Outcome	40	47	Δ = 7 ‡
	95% Confidence Interval			(1, 13)

* WOMAC = Western Ontario McMaster Osteoarthritis Index.
# Scale from 0 (best) to 100 (worst).
† Difference is adjusted using an analysis of covariance (ANCOVA) model with main effects of treatment and center and baseline covariate.
‡ Difference is adjusted using an analysis of covariance (ANCOVA) model with main effects of treatment, center, and indicator of pain in the CMC-1 joint, and baseline as a covariate, and the treatment-by-CMC-1 strata.

2.5. Contraindications

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product[11]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients[11]
- In the setting of coronary artery bypass graft (CABG) surgery[11]

2.6. Study Rationale

This is a study designed to evaluate the therapeutic equivalence and safety of a Diclofenac Sodium Gel in order to facilitate registration of a generic version of Diclofenac Sodium Gel, 1% of Mylan Inc. The Reference Listed Drug (RLD)is Voltaren® Gel (Diclofenac Sodium Topical Gel) 1%. This study will be conducted in male and female subjects with confirmed diagnosis of osteoarthritis of the knee.

2.7. Dosage & Administration

Knee

The proper amount of Diclofenac Sodium Gel should be measured using the dosing card. The dosing card should be used for each application of drug product. The gel should be applied within the rectangular area of the dosing card up to 4 gm line. The dosing card provided with the product can be used to apply the gel. The hands should then be used to gently rub the gel into the skin. After using the dosing card, hold with fingertips, rinse, and dry.

2.8. Risks and Benefits

Mylan [redacted]. has developed the generic formulation of Diclofenac Sodium Gel, 1% which may or may not be effective.

Most common adverse reactions (incidence >2% of patients treated with VOLTAREN® GEL and greater than placebo) are application site reactions, including dermatitis.

Application site reaction reported with diclofenac gel includes: application site dermatitis, application site pruritus, application site erythema, application site paresthesia, application site dryness, application site vesicles, application site irritation and application site papules. [11]

Other adverse reactions includes cardiovascular thrombotic events, GI bleeding, ulceration and perforation, hepatotoxicity, hypertension, heart failure, and edema, renal toxicity and hyperkalemia, anaphylactic reactions, serious skin reactions and hematologic toxicity. Potential benefits include improvement in pain, stiffness and improved physical function associated with OA.

2.9. Non-Investigational Medicinal Products (NIMP)/Rescue Medication – Acetaminophen (paracetamol):

Use[12]*:*

- Temporarily relives minor aches and pain due to:
  - Minor pain of arthritis
  - Muscular aches
  - Backache
  - Pre- menstrual and menstrual pain
  - Common cold
  - Headache
  - Toothache
- Temporarily reduces fever

Warnings

Hepatic Effects[12]*:*

- Severe liver damage may occur if patient will take
  - more than 4,000 mg of acetaminophen (paracetamol) in 24 hours with other drugs containing acetaminophen (paracetamol)
  - 3 or more alcoholic drinks every day while using this product

- Subjects with allergy to acetaminophen (paracetamol)

3. OBJECTIVES

Primary Objectives:

1. To determine the clinical equivalence of Test Drug(Diclofenac sodium gel of 1% of Mylan Inc.) with the Reference Listed Drug (RLD)(Voltaren® Gel 1% of Novartis Consumer Health, Inc.) as measured by mean change from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert (version 3.1) pain score.
2. To establish superiority of the Test Drug and Reference Listed Drug (RLD) over placebo in mean change from baseline in the WOMAC Likert (version 3.1) pain score.

Secondary Objectives:

1. To assess the safety and tolerability of study treatments.
2. To determine the clinical equivalence of Test Drug(Diclofenac Sodium gel) with the Reference Listed Drug (RLD)(Voltaren® Gel) as measured by mean change from baseline in subjects whose baseline WOMAC Likert (version 3.1) pain scores are less than or equal to 10.

4. STUDY DESIGN

Randomized, Double-blind, Multi-centric, Parallel, Active and Placebo Controlled, Three Arm, Clinical Study, with subjects randomized in the ratio of 1:1:1 of Mylan's Diclofenac Sodium Topical Gel 1%, Voltaren® Gel 1% (Reference Listed Drug), and Placebo gel respectively.

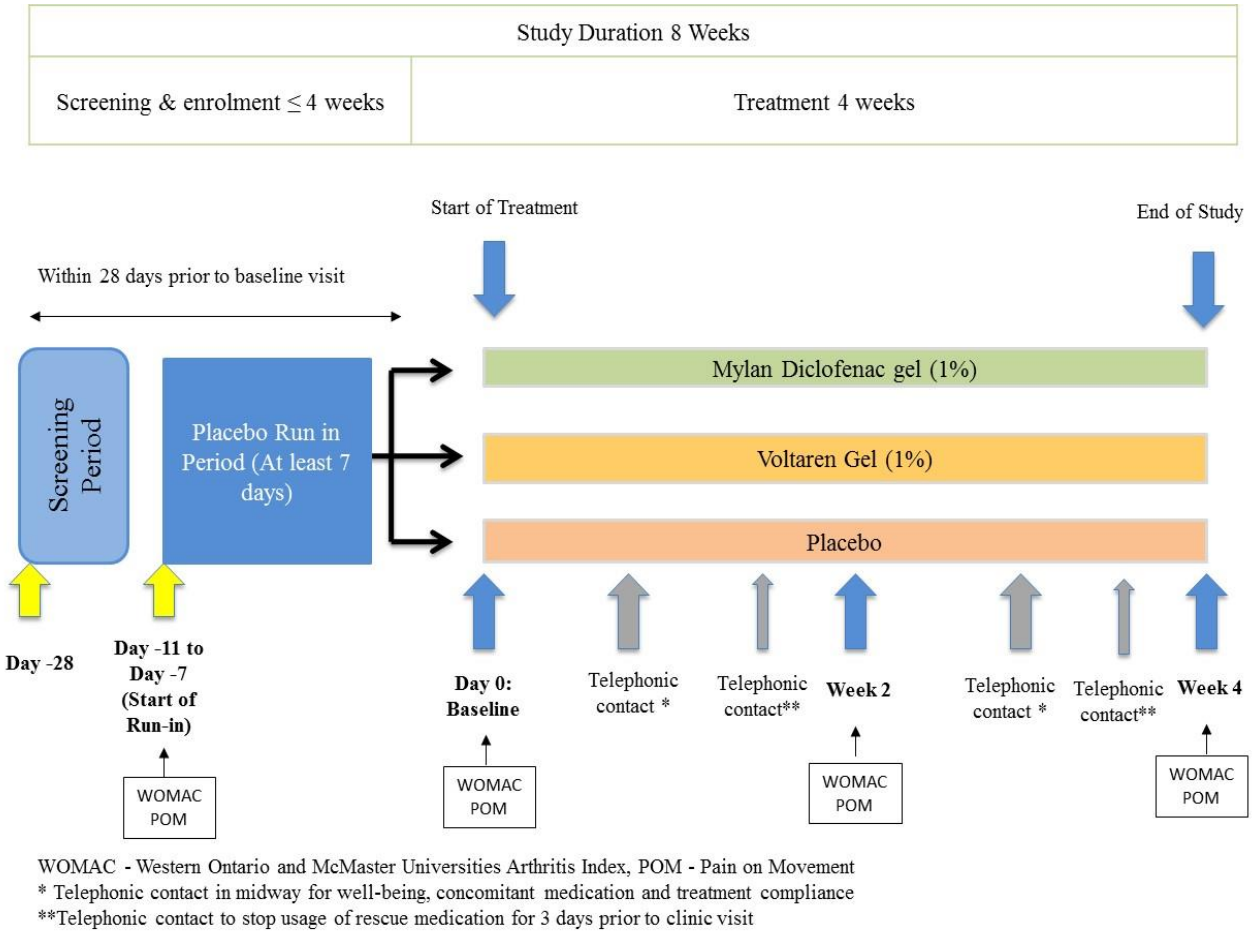
4.1. Study Overview

This is a double-blind, multiple-site, randomized, parallel-design study to investigate the bioequivalence with clinical endpoint of Mylan's Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel, 1% (Novartis US) and to investigate that both the active products are superior to placebo.

Subjects will have to visit the clinic for the following visits during the study –

Visit 1 – Screening visit (within 28 days prior to randomization)
Visit 2 – Start of Placebo Run-in period (Day -11 to Day -7)
Visit 3 – Randomization (baseline) visit (Day 0)
Visit 4 – Interim visit (Week 2/Day 14 ± 4)
Visit 5– End of study (Week 4/Day 28 ± 4)/ Early termination visit

Figure 1: Study Design Flow Chart



After informed consent process and completion of all screening assessments, the eligible subjects will be requested to stop the currently ongoing osteoarthritis drug therapy. The wash out period (run-in period) of 7 days or ≥ 5 half-life of previous osteoarthritis drug therapy, whichever is longer, will be maintained before the baseline visit. Subjects will undergo at least 7 days of placebo run-in period.
In case subject extends run-in period beyond 11 days, continuation of the subject will be decided in consultation with Medical monitor.

The Pain on Movement (POM) score on a Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Likert version 3.1) pain score will be recorded at the start of run-in Period and at the end of run-in Period (i.e. immediately prior to randomization on the day of baseline visit). Recording of the VAS will be done for both the knees and recording of the WOMAC pain score will be done for the target knee.

During the washout period, subjects will undergo a single-blind placebo run-in period where the subjects will not be aware of the placebo nature of the drug. Subjects will be provided with placebo gel for the administration. Approximately 4 gm dose of placebo gel will be applied to the target knee four times daily for at least 7 days. Target knee means the knee which is more painful will be identified during the screening visit. First administration of gel will be done at the study site.

At baseline visit, subjects will be randomly assigned in 1:1:1 ratio to Mylan's Diclofenac Sodium Topical Gel 1%, Voltaren® Gel 1% (Reference Listed Drug) and Placebo. All the subjects will be instructed to apply the gel next day (Day 1) onwards. All subjects will be applying approximately 4 gm dose of either Mylan's Diclofenac Sodium Topical Gel 1% or Reference Listed Drug (RLD)or Placebo gel to the arthritic target knee four times daily for 4 weeks.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Likert version 3.1) pain score for the target knee and pain on movement (POM) on a Visual Analog Scale (VAS) for both the knees will be recorded on Week 2 and Week 4 from the start of the treatment.

Acetaminophen (paracetamol) tablets will be given to the subjects for use as a rescue medication or for the treatment of aches and pains unrelated to knee pain such as headache during treatment period (except 3 days prior to Visit 4 and Visit 5). Maximum allowed dose of acetaminophen (paracetamol) will be 2 gm/day. Consumption of rescue medications in terms of number of tablets consumed will be monitored.

Subject diary will be provided to subjects to record study medication gel application, rescue medication, side effects, and concomitant medication details. Subjects will be trained regarding how to use the subject diary. Subject diary will be used to evaluate drug application compliance. Subjects will be trained via a detailed and translated instruction subject diary on how to administer the study drug.

Physical examination will be conducted during each visit (except at the start of run-in period visit). Application site reaction assessment will be conducted on each visit after start of run-in period.

A standard 12-lead ECG will be recorded after 5 minutes of rest in the supine position on screening visit and on end of study visit. Vital signs will be measured after 5 minutes of rest (sitting) on each visit.

Serum pregnancy test for females of childbearing potential will be performed at screening and end of treatment visit. The urine pregnancy test can be performed if clinically indicated during other visits. If urine pregnancy is found to be positive, serum pregnancy will be drawn and analyzed for

confirmation. If serum pregnancy test will found positive then patient will be excluded from the study and followed up.

Laboratory assessments like hematology and biochemistry will be performed during screening and end of study. The hematology and biochemistry at screening to be performed within 14 days of baseline visit. If the gap between lab assessments and baseline visit will be more than 14 days, the lab assessments will be repeated at baseline visit. Laboratory investigations (if clinically significant) can be repeated once as per investigator's discretion.

Principal investigator or designee will contact the subjects approximately midway between the visit 3-4 and visit 4-5 for assessment of the well-being, adverse event, concomitant medication, and treatment compliance.
Additional telephonic contact to reiterate the instructions regarding the use of rescue medications during 3 days prior to visits 4 and 5 will be done. Use of rescue medications by subjects during this period for intolerable pain will require rescheduling the visits in such a way that visits happen after at least 3 days of stopping rescue medication and subjects will be required to inform the site about the rescue medication use. The same will be documented in the source notes.

Statistical analysis will be done as per the Section 12.0.

5. STUDY POPULATION

1212 subjects will be randomized in the study.
Patients are eligible for enrollment into the study if they meet all of the inclusion criteria and do not meet any of the exclusion criteria.

5.1. Inclusion Criteria

1. Healthy male or non-pregnant female aged ≥ 35 years with a clinical diagnosis of OA of the knee according to the American College of Rheumatology (ACR) criteria[2] i.e. Knee pain along with at least 3 of the following 6 criteria
    a. Age > 50 years
    b. Stiffness < 30 minutes
    c. Presence of crepitus
    d. Bony tenderness
    e. Bony enlargement
    f. No palpable warmth
2. Symptoms in target knee for at least 6 months prior to screening
3. Knee (not referred) pain in target knee for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.)
4. Pain in the target knee requiring the use of NSAIDs or acetaminophen/paracetamol (topical or oral treatments).

5. Subject having an X-ray of the target knee, taken no more than 1 year before baseline, showing evidence of OA with Kellgren-Lawrence grade 1-3 disease.
6. After discontinuing all pain medications (placebo run – in period) for at least 7 days, had at least moderate pain on movement (POM) for target knee, defined as a baseline score of ≥ 50 mm on a 0-100 mm Visual Analog Scale (VAS) immediately prior to randomization
7. After discontinuing all pain medications (placebo run – in period) for at least 7 days has a baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Likert (version 3.1)) pain subscale of ≥9 immediately prior to randomization.
8. Able to tolerate rescue medication with acetaminophen (paracetamol) taken as l-2 tablets up to a maximum 2 gm per day for the duration of the study.
9. Subjects who can read and understand WOMAC pain sub scale.
10. If female, patient must be either postmenopausal for at least one year prior to randomization, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or practicing the following methods of birth control:
    a) Oral Contraceptives or Intrauterine Device in place for at least 3 months prior to the start of the study and remaining in place during the study period, or
    b) Double Barrier methods containing or used in conjunction with a spermicidal agent, or
    c) Contraceptive Patches/ Implants, or
    d) Abstinence: Subjects who will be practicing abstinence will agree to have a documented second acceptable method of birth control if the subject become sexually active during the course of her study participation.

5.2. Exclusion Criteria

1. Pregnant or lactating or planning to become pregnant during the study period.
2. X-ray showing evidence of OA with Kellgren-Lawrence grade 4 disease.
3. History of OA pain in the contralateral knee requiring medication (OTC or prescription) within 1 year prior to screening.
4. After discontinuing all pain medications (placebo run-in period) for at least 7 days, had a baseline score of ≥ 20 mm on a 0-100 mm Visual Analog Scale (VAS) for the contralateral knee immediately prior to randomization.
5. History of OA of either Hip or Hands
6. History of secondary OA (e.g. congenital, traumatic, gouty arthritis), rheumatoid arthritis.
7. History of chronic inflammatory disease (e.g., colitis) or fibromyalgia.
8. History of Drugs or Alcohol abuse within the previous year.
9. Symptomatic peripheral vascular disease of the study leg (prior or current).
10. Any musculoskeletal condition that would impede measurement of efficacy at the target knee.
11. History of regular headaches or backache which warrants often use of acetaminophen (paracetamol) within the previous year.

12. Concomitant skin disease at the application site which may affect study drug application or tolerability evaluation.
13. History of active asthma within the previous year that may require periodic treatment with systemic steroids during the study period (note: inhaled steroids for this condition are allowed).
14. History of aspirin sensitive asthma.
15. History of uncontrolled hypertension (blood pressure more than 150/100 mm of Hg) in spite of treatment within the previous year.
16. History of myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function (Serum creatinine > 1.5 x ULN) or liver disease within the previous year.
17. History of coronary artery bypass graft within 6 months of screening.
18. History of gastrointestinal bleeding or peptic ulcer disease in last one year.
19. Known allergy to aspirin, nonsteroidal anti-inflammatory drugs (NSAID) or acetaminophen (paracetamol).
20. Elevated transaminases (≥ 3 times ULN) and Hemoglobin < 9.0 g/dL at screening.
21. Viscosupplementation in any joint including the target knee within 6 months prior to screening
22. Receiving physical therapy (at an outpatient/clinic setting) for the lower extremities or having received physical therapy for the lower extremities within 1 month before screening.
23. Use of anticoagulants, ACE-inhibitors, cyclosporine, diuretics, lithium, or methotrexate prior to 30 days of screening.
24. Concomitant use of intra articular corticosteroids, systemic corticosteroids, topical corticosteroids, or immunosuppressive drugs or their use prior to 30 days of screening.
25. Concomitant acetylsalicylic acid therapy other than a stable low dose used for cardiac prophylaxis (maximum 162 mg daily)[3] taken for at least 3 months prior to enrollment and maintained throughout the duration of the study.
26. History of major surgery or previous damage to the study knee at any time, or minor knee surgery (e.g. any surgery other than major surgery including, but not limited to, cartilage repair, collateral ligament repair, or arthroscopic debridement) to the study knee within 1 year prior to screening.
27. Known history of positive HIV, HCV, or HBsAg.
28. Tense effusion requiring aspiration.
29. Subjects who have been treated with an investigational drug or investigational device within a period of 30 days prior to enrollment.
30. Any other acute or chronic illness that could compromise the integrity of study data or place the subject at risk by participating in the study.

6. RANDOMIZATION AND BLINDING PROCEDURES

6.1. Randomization Procedure

A computerized randomization will be generated by an independent third party (not involved in the packaging and labelling of the study medication).

Subjects will be randomly assigned in 1:1:1 ratio in three groups. Treatment allocation can be either Mylan's Diclofenac Sodium Topical Gel 1%, Voltaren® Gel 1% (Reference Listed Drug), or Placebo. A balanced randomization schedule will be generated using SAS® software (Version: 9.1or higher; SAS Institute Inc., USA). The randomization code will be held by an independent third party throughout the conduct of the study in order to minimize bias.

A sealed copy of the randomization code for each kit provided under separate cover inside the block will be retained at investigational site. It should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

6.2. Blinding Procedure

Placebo run-in period will be single blinded in which subjects will not be aware of the treatment given.

Treatment period will be double blinded in which all the investigators, subjects, site staff, CRO team, study monitors, laboratory personnel and/or other designated individuals will be blinded to the medication codes. The formulation of test, reference and placebo investigational products would be identical in appearance to make any difference in treatment less obvious to the subjects and to maintain adequate blinding of evaluators.

Unblinding will be performed by a designated person in case of SAE or other significant events (Refer section 11.2.5.3). The event of unblinding shall be documented in the source notes.

Mylan Product Safety and Risk Management (PSRM) can unblind the treatment assignment for any subject with a SAE which qualifies for the unblinding based on country specific regulatory requirements.

The event of unblinding shall be documented in the source notes. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

If a subject's treatment assignment is unblinded for any reason then the subject should be withdrawn from the study.

7. STUDY TREATMENT, DESCRIPTION AND ALLOCATION

7.1 Investigational Medicinal Products and Non - Investigational Medicinal Products (IMP and NIMP)

Investigational Medicinal Products (IMP)

The study medication supplied by the sponsor will consist of:

Treatment Arms	Intervention
Test product:	Diclofenac Sodium Gel, 1% manufactured by Mylan Inc.
Reference product:	Voltaren® Gel (Diclofenac Sodium Topical Gel) 1% manufactured by Novartis Pharma Produktions GmbH, marketed by: Endo Pharmaceuticals Inc., Malvern, PA 19355
Placebo formulation:	Placebo gel [redacted].

Identical dosing cards will be provided along with the investigational medicinal products.

Non-Investigational Medicinal Products (NIMP)

Acetaminophen (paracetamol) tablets will be given to all the subjects baseline for use as a rescue medication or for the treatment of aches and pains unrelated to knee pain such as headache during treatment period.

7.2 Investigational Product Labeling, Packaging & Formulation

Study drugs will be packaged and labeled based on the randomization schedule generated prior to the start of the study. The investigator will be overall responsible for ensuring that IPs are stored in a safe, limited access location, as per the condition noted in the label. Each site will receive the pre-labeled study drugs for the run-in period and treatment period.

Labelling text will be compliant with local regulatory requirements. The label should include but not be limited to: Sponsor name/address, Dosage, route of administration, name/strength, batch number/code, study reference or protocol number, kit's number, directions for use, statement 'for clinical trial use only', storage conditions, expiry/use by date.

At the start of placebo run-in period and at baseline visit, each subject will receive the study drugs and at the baseline visit, subjects will receive the rescue medications.

Formulation Details

Test Formulation	Active ingredient: Diclofenac sodium Inactive ingredients: [redacted]
Reference Formulation	Active ingredient: Diclofenac sodium Inactive ingredients: Carbomer homopolymer Type C, cocoyl caprylocaprate, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution
Placebo Formulation	It will contain all the excipients (inactive ingredients) present in the test formulation.

7.3 Storage Conditions

Study medication should be stored, prior to dispensing, at controlled temperature 20°C to 25°C (68°F to 77°F) in a locked, limited access area at the study center. Do not freeze the product. Dosing card should be stored along with study medication. After dispensing, the subject will be instructed to store the medication at 20°C to 25°C (68°F to 77°F) [USP Controlled Room Temperature]. Used/unused medications except the retention samples, will be handled as per instructed by the sponsor.

7.4 Investigational Product Handling and Management

The medication will be supplied in tubes as a kit. The tubes will be packed and labeled according to the randomization scheme generated prior to the start of the study. The containers/kit should not be opened by the subject at the study center.

Details of the IP handling will be described in 'IP Handling Work Instruction'.

7.5 IP Retention Requirements

The sponsor will supply sufficient quantities of the study formulation for the following: 1) completion of the study and 2) retention, as per applicable regulations. All drug supplies provided for this study will be stored in a secure area with restricted access, under storage conditions described in the reference drug package labeling.

Details of the IP retention will be described in 'Investigational Product Retention Plan'.

Records will be made of receipt and dispensing of study drugs supplied. It is the responsibility of the Sponsor to ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices (cGMP) and are suitable for human use.

Upon completion or termination of the study, a sample of all study supplies will be retained for a period of at least 5 years following the date on which the study is approved by USFDA or, if the study is not approved, at least 5 years following the date of completion of the study in which the investigational products were used. Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor or CRO at any time.

7.6 Study Medication Administration

At the start of the placebo run-in period, placebo gel will be dispensed and during the treatment period, Mylan's Diclofenac Sodium Topical Gel 1%, Voltaren® Gel 1% (Reference Listed Drug), and Placebo gel will be dispensed to the qualified subjects for the application of gel to the target knee. Target knee means the knee, which is more painful, will be identified during the screening visit. First administration of the study drug at the start of placebo run-in period will be supervised at the study center, with subsequent applications self-administered on an outpatient basis.

Subject diary will be given at the start of the placebo run-in period and treatment period to the subjects containing instructions related to the proper administration method (see Appendix I).

Method of application during run-in period and treatment period:

Study participants will have to apply 4 gm of study medication to the affected area of target knee 4 times daily. The proper amount of gel will be measured using the dosing card. The gel will be applied within the rectangular area of the dosing card up to 4 gm line. [redacted].

[redacted]

Rescue Medication Administration:
Subjects will be allowed acetaminophen (paracetamol) tablet as rescue medication on an as-needed basis (up to 2 gm/ day) during the treatment period, except for the at least 3 days prior to each clinic visit.

7.7 Subject withdrawal Criteria

Subjects will be discontinued from the study for any of the following reasons:

- If the subject withdraws his or her consent for any reason.
- If the subject's condition has worsened to the degree that the investigator feels, it is unsafe for the subject to continue in the study.
- If the subject's drug code is unblinded.
- If an adverse event occurs for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued.
- If the subject with a score of ≥ 20 mm on a 0-100 mm Visual Analog Scale (VAS) for the contralateral knee
- If there is a significant protocol violation.
- If the subject is lost to follow-up. (The investigator will document all attempts to reach the subject by telephone and/or in person in source documents before considering that subject lost to follow-up.)
- If the female subject becomes pregnant.
- Treatment failure based on investigator's discretion.

- Administrative reasons.

The reasons for a subject being discontinued will be documented in the source notes and captured in case report form.

If a subject is discontinued from the study for any reason, the Day 28/ Early Termination Visit procedures should be completed and any outstanding data and study drug should be collected. Data, in addition to the reason for discontinuation and the date of removal, will be captured on the End of Study section of eCRF.

In the event that a subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a subject, the investigator must strive to follow the subject until the adverse event has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

Should a serious adverse event be noted, procedures stated in Section 11.2.2 must be followed.

7.8 Premature Termination of Study in a Study Center

The Sponsor reserves the right to discontinue the study at any time. The reasons will be discussed with the Investigator. A study site may also be discontinued by the Sponsor for significant deviations from the protocol or due to difficulties experienced in running the study at that center.

The Sponsor may terminate this study in one particular or several study center(s) for one of the following reasons:

- Non-compliance with GCP and/or regulatory requirements
- Center cannot recruit an adequate number of patients
- False documentation in the eCRF due to carelessness or deliberately
- Inadequate co-operation with the Sponsor or its representatives
- The Investigator requests closure of his/her study center

If the study is prematurely terminated in one or more study centers, all Investigators have to inform their patients and take care of appropriate follow-up and further treatment of the patients. Ethics Committees and regulatory authorities will be informed about the reason and time of termination according to the applicable laws and regulations.

7.9 Termination of the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Mylan [redacted], [redacted]. In addition, Mylan [redacted] retains the right to discontinue development of generic formulation of diclofenac gel at any time.

If a study is prematurely terminated or discontinued, Mylan [redacted] will promptly notify the investigator. After notification, the investigator shall contact all participating subjects. As directed

by Mylan Laboratories Limited, all study materials must be collected and all CRFs completed to the greatest extent possible.

7.10 Treatment Compliance

A Subject Diary will be provided to all subjects where it is required to document the date and time of application of the medication. In the subject diary, subjects will also note of any adverse event observed, date and time of rescue medication administration and any concomitant medication taken or changed.

Compliance will be determined from the subject diary, which the subject will be trained and instructed to use to record all doses, as well as all missed doses. The number of missed and additional doses will be captured on the compliance page of the eCRF.

The used study medication tubes will be returned to the study site at appropriate visits or early termination or as applicable.

Subjects who are not compliant with application will be re-counseled during the study visits.

Subjects who will take less than 75% (<84 applications) of total study drug during the study will be considered non-compliant and discontinued from the study. Subjects who will take more than 125% (>140 applications) of study drug are also considered non-compliant and the same subjects will not considered for the Per-protocol (PP) population.

7.11 Study Medication Accountability

When a drug shipment is received at a study center, the investigator/designee shall sign the receipt form provided with the shipment.

Subjects shall be instructed to return used, partially used, or unused study medication kits to the study center staff so that any remaining drug supplies can be accounted for and noted in the log for accountability.

7.12 Return of Clinical Supplies

All used and unused kits of study medication will be handled as per Sponsor's instructions in IP handling plan after completion of the study.

7.13 Concomitant/Prohibited Treatment:

Any medication other than study drug, either prescription drug or OTC drug will be treated as concomitant medication.

All medications taken on a regular basis should be recorded in source data.

If drug therapy other than that specified in the protocol is required, it should be documented and have to be pre-approved by the investigator (if required in consultation with medical monitor/sponsor) prior to the subjects usage. Further, the Investigator (if required in consultation with medical

monitor/sponsor) decide the course of action for that participant based on the time the medication was administered and its pharmacology.

The following are **prohibited** during this study:

1. Any other topical or intraarticular products applied to the target site.
2. ACE-inhibitors, anticoagulants, cyclosporine, diuretics, lithium, methotrexate or oral NSAIDs.
3. Muscle relaxants
4. Sedative/hypnotics (stable dose for at least 14 days prior to baseline visit will be allowed)
5. Chondroitin/glucosamine
6. Opioids
7. Glucosamine
8. Chondroitin
9. Use occlusive bandages, ultrasound, transcutaneous electrical stimulation or any alternative therapies such as acupuncture, homeopathy or mesotherapy
10. Systemic corticosteroids or immunosuppressive drugs.
11. Pain medication other than acetaminophen (paracetamol) including topical NSAIDs
12. Non-pharmacological devices for knee pain like knee brace, herbal remedies.

Physical therapy will be permitted if this started at least 1 month before screening but cannot be initiated or changed during the study. Exercise regimens and the application of heat or cold will not be started, discontinued, or changed during the study.

Permitted Medications

Subjects will be allowed to continue taking stable (non-analgesic) medications that would not interfere with the metabolism of diclofenac.

Concomitant use of acetylsalicylic acid for cardiac prophylaxis with maximum 162 mg daily will be allowed during the study if the therapy is stable for at least 3 months.

7.14 Rescue medication

Subjects will be permitted to take acetaminophen (paracetamol) tablet as needed during the treatment period. Any use of rescue medication will be recorded by the subject in the subject diary (e.g., Date and time). [redacted]. Rescue medications will not be permitted within 3 days of the assessments during treatment period. Use of rescue medications by subjects during this period for intolerable pain will require rescheduling the visits in such a way that visits happen after at least 3 days of stopping rescue medication and subjects will be required to inform the site about the rescue

medication use. Site staff will telephonically remind to subjects regarding stop usage of rescue medication before the visit and next visit date. The use of rescue medication will be compared between treatment groups.

8 EFFICACY ASSESSMENTS

8.1 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert Scale 3.1

Western Ontario and McMaster Universities Osteoarthritis Index is used to assess pain, stiffness, and physical function in subjects with hip and / or knee osteoarthritis (OA).
The WOMAC consists of 24 items divided into 3 subscales[13]:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties

Among all the 3 subscales, pain score will be used during the study.
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score will be recorded at the start and at the end of run-in Period (i.e. immediately prior to randomization on the day of baseline visit); and on Week 2 and Week 4 for target knee after start of treatment.

WOMAC pain score (pain score = 0 to 20), will be determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1, 'moderate'=2; 'severe'=3; 'extreme'=4). The questions pertain to the amount of pain the subject is currently experiencing in the target knee [i.e., 'How much pain do you have' when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'at night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)]. WOMAC pain score will be given to the subject along with the necessary instruction on the each visit.

8.2 Pain on movement (POM) after 100 Meter Walk on a Visual Analog Scale (VAS)

Pain on movement (POM) on a Visual Analog Scale (VAS) will be determined by the subject's responses at the start and at the end of run-in Period (i.e. immediately prior to randomization on the day of baseline visit); and on Week 2 and Week 4 after start of treatment for the both the knees. The subject will be asked to place a mark to the VAS line at the point that represents pain intensity. The VAS score will be determined by measuring in millimetres from the left hand end of the line to the point that the patient marks by site staff. The calibrated ruler will be used to estimate VAS score.[14]

VAS scale:

9 SAFETY ASSESSMENTS

9.1 Adverse Events

Safety will be determined by monitoring adverse events (AEs), which will be classified using MedDRA (Medical Dictionary for Regulatory Activities) terminology.

9.2 Medical History

A complete medical history, including a complete review of all current and past diseases and their respective treatments, must be done on screening visit.

9.3 Physical Examination

The investigator or sub-investigator must perform a physical examination on screening, baseline visit, interim visit (on day 14) and end of study visit.
Joint examination of the affected knee will be performed during the screening includes following:

- Recording of affected knee (left/right)
- Receiving any physical therapy at screening
- Subjects with periarticular pain
- Range of motion

⇒ Extension (degree)
⇒ Neutral (degree)
⇒ Flexion (degree)

- Tenderness on pressure (scale: 0 = none, 1=mild, 2=moderate and 3=severe)

⇒ Joint space medially
⇒ Joint space laterally
⇒ Patella medially
⇒ Patella laterally

- Swelling of joint capsule(scale: 0 = none, 1=slight, 2=moderate and 3=severe)
- Joint effusion (Yes/No)

Vital signs (heart rate, respiratory rate, body temperature and blood pressure) will be measured after 5 minutes of rest (sitting) on each visit.

A standard 12-lead ECG will be recorded after 5 minutes of rest in the supine position on screening visit and on end of study visit.

X-ray of target knee will be performed on screening if not performed for more than 1 year prior to baseline.

9.4 Application Site Reaction

Application site reaction will be assessed on each visit after start of run-in period to evaluate the adverse events if any.

9.5 Laboratory Tests

Following laboratory tests will be performed at screening and at the end of the study:

Hematology				
Hemoglobin	Total RBC count	Total WBC count	Platelet count	
Differential Leukocyte count:				
Neutrophils	Lymphocytes	Eosinophils	Monocytes	Basophils
Blood Chemistry				
Alkaline Phosphatase	Serum Creatinine	Random Glucose	SGPT & SGOT	
Serum Bilirubin				

If the gap between screening laboratory assessments (hematology and biochemistry) and baseline visit is more than 14 days, the lab assessments should be repeated at baseline visit

If warranted, other tests or examinations may be performed at the discretion of the Principal Investigator. Approximately 20 ± 5 ml of blood will be withdrawn during screening visit and at the end of study visit to perform above mentioned Clinical Laboratory Tests.

9.6 Pregnancy Test

Serum Pregnancy Test for females of childbearing potential will be performed during screening visit and at the end of study or early termination visit. The urine pregnancy test can be performed if clinically indicated during other visits. If urine pregnancy is found to be positive, serum pregnancy will be done for confirmation. If serum pregnancy test will found positive then patient will be excluded from the study and followed up.

Acceptable forms of contraception include the following:

- Oral Contraceptives or Intrauterine Device in place for at least 3 months prior to the start of the study and remaining in place during the study period, or
- Double Barrier methods containing or used in conjunction with a spermicidal agent, or
- Contraceptive Patches/ Implants, or
- Abstinence: Subjects who will be practicing abstinence will agree to have a documented second acceptable method of birth control if the subject become sexually active during the course of her study participation.

10 SCHEDULE OF ACTIVITIES: (VISIT SCHEDULE)

10.1 Visit 1: Screening Visit (within 28 days prior to randomization)

- **Informed Consent:** Subjects must provide a signed, IEC/IRB approved written informed consent. No study related procedures or activities will be performed until each subject is fully informed and the consent form is signed and dated. All subjects will be given a copy of the signed and dated consent form.
- **Inclusion/Exclusion Criteria Review**
- **Demographic Data** (Height, weight, age, sex, ethnicity etc.)
- **Medical History.** A complete medical history will be recorded. Information regarding the subject's current and past medical conditions will be captured including surgical procedures.
- **Physical Examination (along with baseline joint examination)and Vital Signs**
- **Evaluation of ACR criteria for OA**
- **Laboratory Tests**
- **X-ray of target knee, evaluation as per the Kellgren-Lawrence grading** (See Appendix III)
- **ECG**
- **Serum Pregnancy Test** (for all females of childbearing potential)
- **Assess Adverse Events** (after signing of the ICF)

10.2 Visit 2: Start of Placebo Run-in Period (Day -11 to Day -7)

- **Discontinuation of current osteoarthritis therapy**
- **Vital Signs**
- **Inclusion/Exclusion Criteria Review**
- **Urine Pregnancy Test** (for all females of childbearing potential) if clinically indicated
- **Pain on Movement (POM) assessment in both the knees- 100mm VAS**
- **WOMAC pain score assessment of the target knee**
- **Study Medication and Subject Diary Dispensing for Run-in Period:** Placebo gel for run-in period will be dispensed by the site staff to qualified subjects. A subject diary, containing instructions for subjects, will be dispensed to each qualified subject. First administration of gel will be supervised at the study center.
- **Instructions on placebo application and storage**
- **First placebo gel application at the site**

- **Assess Adverse Events**
- **Assessment of Concomitant Medications.**

10.3 Treatment Period Visits

10.3.1 Visit 3 (Baseline): Day 0

The following procedures will be performed at the Randomization Visit:

- **Physical Examination and Vital Signs**
- **Inclusion/Exclusion Criteria Review**
- **Urine Pregnancy Test** (for all females of childbearing potential) if clinically indicated.
- **Laboratory investigations (if not performed within 14 days of baseline visit)**
- **Pain on Movement (POM) assessment in both the knees- 100mm VAS**
- **WOMAC pain score assessment of the target knee**
- **Subject diary (placebo run-in period) review and its collection**
- **Assessment of treatment compliance**
- **Application site reaction assessment**
- **Study medication and Subject diary for treatment period dispensing:** Study medication for treatment period will be dispensed by the site staff to qualified subjects. A subject diary, containing instructions for subjects, will be dispensed to each qualified subject.
- **Instructions on study medication application and Storage**
- **Collection of the unused IP dispensing during placebo run-in period**
- **Rescue medication dispensing**
- **Assess Adverse Events**
- **Assessment of Concomitant Medications**

10.3.2 Visit 4: Interim Visit (Week 2/Day 14 ± 4)

The following procedures will be performed.

- **Physical Examination and Vital signs**
- **Urine Pregnancy Test** (for all females of childbearing potential) if clinically indicated.
- **Subject diary review**
- **Assessment of treatment compliance**

- **Pain on Movement (POM) assessment in both the knees- 100mm VAS**
- **WOMAC pain score assessment of the target knee**
- **IMP dispensing**
- **Collection of the unused IPs**
- **Rescue medication dispensing (if required)**
- **Application site reaction assessment**
- **Assess Adverse Events**
- **Assessment of Concomitant Medications.**

10.3.3 Visit 5: End of Study (Week 4/Day 28 ± 4)/Early Termination Visit

The following procedures will be performed.

- **Physical Examination and Vital Signs**
- **Serum Pregnancy Test** (for all females of childbearing potential)
- **Laboratory investigations**
- **ECG**
- **Pain on Movement (POM) assessment in both the knees- 100mm VAS**
- **WOMAC pain score assessment of the target knee**
- **Subject diary (treatment period) review and its collection**
- **Assessment of treatment compliance**
- **Collection of the unused IPs and rescue medication**
- **Application site reaction assessment Collection of unused medications (IP/NIMPs)**
- **Assess Adverse Events**
- **Assessment of Concomitant Medications**

Note:

⇒ Additional assessments could be performed as per Investigators' discretion during the study.
⇒ All the subjects will be instructed to apply the gel next day (Day 1) onwards.
⇒ Telephone contact: Principal investigator or designee will contact the subjects approximately midway between the visit 3-4 and visit 4-5 for assessment of the well-being, adverse event, concomitant medication, and treatment compliance. Additional telephonic contact will be done

to remind the subject regarding stoppage of rescue medication usage prior to scheduled visits (Visit 4, and Visit 5). The same will be documented in the source notes.

⇒ In case subject extends run-in period beyond 11 days, continuation of the subject will be decided in consultation with Medical monitor.

10.4 Unscheduled Visit

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. If the investigator assesses the subject's condition at any time and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study (including suspected use of placebo), the subject may be discontinued from the study as treatment failure, and a standard of care treatment may be advised at the investigator's discretion.

If subject is discontinued early from the study, Day 28/ Early Termination Visit activities will be performed (see Appendix II).

11 ADVERSE EVENT REPORTING

11.1 Assessment of Safety

11.1.1 Safety Parameters

Safety may be assessed by the monitoring of adverse clinical events, electrocardiograms, clinical laboratory evaluations and physical examinations. All adverse events occurring during the study must be recorded according to Section '**Adverse Events**'.

11.2 Adverse Events

The adverse event collection period begins at signing of informed consent and continues until 28 days after the last dose. Adverse events occurring during this period need to be reported to the sponsor according to Section '**Documentation of Adverse Events**'.

The investigator is also responsible for notifying the sponsor if he/she becomes aware of any adverse event after the study period has ended and it is considered related to the study medication (i.e. an adverse drug reaction).

Once an AE is detected, it should be followed until its resolution or until it is judged by the principal investigator to be stable or permanent.

11.2.1 Definitions

Adapted from ICH Harmonised Tripartite Guideline: Clinical Safety Data Management Definition and Standards for Expedited Reporting: E2A

Adverse Event:
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with, whether or not related to the product.

Examples of adverse events include but are not limited to:

- A new disease or exacerbation of an existing disease. Note: worsening of osteoarthritis pain of the knee (disease progression), the condition under study, will not be recorded as an adverse event.
- A recurrence of an intermittent condition (e.g., migraine) not present at baseline;
- A deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is considered clinically significant by the investigator or associated with symptoms or leads to a change in study treatment, concomitant therapy, or discontinuation from study drug;
- A symptom or medical complication related to a protocol-mandated intervention, including screening and run-in period procedures.

Serious Adverse Event:
Any adverse event that:

- Results in death
- Is life-threatening – means 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 – any patient admission to a healthcare facility, even if for less than 24 hours. A planned hospitalization required by the protocol or scheduled prior to study initiation does not constitute an SAE
- Prolongs hospitalization – any extension of hospitalization
- 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 or prevent everyday life functions but do not constitute a substantial disruption
- Is a congenital anomaly/birth defect. A pregnancy during the study meets the seriousness criteria in the following cases: miscarriage, congenital anomaly, neonatal death, infant death

- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other listed outcomes listed in the definition above? Examples of such events are any cancer, 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.

Treatment emergent adverse event:
Any adverse event that occurs after the first dose of study medication through 28 days after the last dose.

Unexpected adverse event/Adverse Drug Reaction:

An expected AE or adverse drug reaction (ADR) is defined as one whose nature or severity is consistent with the reference safety information in the approved label.
An AE is considered unexpected if the nature or severity is not consistent with the applicable product reference safety information. Reports that add significant information on specificity or severity of a known, already documented ADR constitute unexpected events.

11.2.2 Documentation of Adverse Events

The investigator or designee must record all adverse events reported by subjects that have occurred during the adverse event collection period of the study.

Adverse events should be solicited from subjects through open-ended questions, and as appropriate, by examination. Subjects should normally be evaluated for adverse events following drug administration and prior to discharge from the clinic. The subject should also be queried for any previously unreported adverse event as part of study exit procedures.

All adverse events, whether or not caused by the study drug, will be recorded on source documents and reported to the Sponsor as per Section 11.2.5. The information in the source document will include:

- The date/time of onset of any new adverse event or the worsening of a previously observed adverse event or worsening of any previously existing disease
- The event in standard medical terminology
- The date of resolution of the adverse event, when applicable
- The relationship of the adverse event to the study drug(s)
- The severity of the adverse event

- Seriousness of the adverse event
- Description of action taken in treating the adverse event and/or change in study drug administration or dose

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs. The following are examples of laboratory abnormalities that would normally qualify as adverse events:

- The abnormality suggests a change in disease severity and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

11.2.3 Relationship of Adverse Experiences to the Study Drug

The Investigator is responsible for assessing relationship of adverse events to study medication (e.g., causality assessment). Factors that need to be considered when making a causality assessment include: the temporal relationship (e.g., time to onset); the clinical and pathological characteristics of the events; pharmacological plausibility; exclusion of confounding factors (medical and medication history); drug interactions; dechallenge/rechallenge, and dose relationship, etc..

A suspected relationship (definite, probable, possible) between the events and the study medication means in general that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality.

The Investigator is responsible for assessing relationship of adverse events to study medication in accordance with the following definitions:

Definite – causal relationship is certain (e.g., the temporal relationship between drug exposure and the AE onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary).

Probable – high degree of certainty for causal relationship (e.g., the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to dechallenge (rechallenge is not required), and other causes have been eliminated or are unlikely).

Possible – causal relationship is uncertain (e.g., the temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, dechallenge information is either unknown or

equivocal, and while other potential causes may or may not exist, a causal relationship to study drug does not appear probable).

Assessments of Unlikely and Unrelated **do not** meet the threshold for reasonable suspected causal relationship and are therefore classified as Unrelated for regulatory reporting and within a binary scale of Related/Not Related.

Unlikely – Temporal relationship between drug administration and event onset is improbable, and/or another explanation is more likely such as disease, environment, other drugs etc. Does not represent a known reaction to study drug.

Unrelated/Not related – no possible relationship (e.g., the temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible).

11.2.4 Severity of the Event

The intensity or severity of AEs will be graded as follows:

- **Mild**- awareness of sign or symptom, but easily tolerated. Not expected to have a clinically significant effect on the subject's overall health and well-being. Does not affect daily activities. Not likely to require medical attention.
- **Moderate** - discomfort enough to cause interference with usual daily activities or affects clinical status. May require medical intervention and/or prescription drug therapy.
- **Severe** - incapacitating or significantly affecting clinical status. Severely limits daily activities. Medical intervention, prescription drug therapy and/or hospitalization required.

Note that the term "severe" is a measure of intensity; thus, a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe, but may not be clinically serious. Likewise, mild or moderate events could, under some circumstances, result in a serious outcome as defined above.

11.2.5 Expedited Reporting of Serious Adverse Events

In addition to standard documentation of adverse events in the source and CRF, serious adverse events require immediate notification to Mylan Product Safety and Risk Management (PSRM). "Immediate" is defined as within 24 hours of the investigator's or site staff's knowledge of the event. Serious adverse events are defined in section 11.2.1 '**Serious Adverse Events**'.

The SAE Reporting Form is to be completed for all serious AEs, signed by the investigator, and emailed or faxed with supporting documentation (e.g. case report forms, hospital records, laboratory reports, etc.). Subject identity details (such as but not limited to name or clinic/hospital number) must not be visible on SAE forms or any supporting documentation provided by the Investigator. Any personal information on supporting documents should be redacted before submission to Mylan. **The**

study specific subject ID must be recorded on every page of the SAE report form and supporting documents sent to Mylan.

The investigator will include a narrative description of the serious adverse event(s) that discusses:

- Study medication(s) administered, including dates
- Date and time of the onset of the serious adverse event
- Signs and symptoms
- Description of the event in standard medical terminology
- Date the event resolved or outcome of the event at last observation
- Laboratory and/or confirmatory tests
- Investigator's assessment - the attribution of the adverse event to the study drug(s) or possible alternative etiologies for the event. If considered related (i.e. definite, probable, possible) to the study medication, the rationale for suspecting an adverse drug reaction should be provided
- Description of action taken in treating the adverse event and/or change in study drug administration or dose

The report form must also contain the subject's demographic information, medical history, and concomitant medication at the time of the event.

All communication of AE/SAE information will be in English.

All SAEs must be sent within 24 hours of awareness to:

Mylan [redacted]

Note: Email is the preferred method of communication

[redacted]

11.2.5.1 Follow-up of Serious Adverse Events

The Investigator is responsible for collecting and forwarding to Mylan PSRM any required information not available at the time of the initial report as well as the final outcome of the SAE.

Follow-up information to a SAE report shall be submitted to Mylan's PSRM department by the investigator as soon as the relevant information is available and reviewed by the investigator. Relevant information such as discharge summaries, autopsy reports, and medical consultations shall be reviewed in detail by the Investigator for important new information. The Investigator shall comment on any event, abnormal laboratory result, or any other finding, noting whether it shall be considered a

serious or non-serious AE or considered part of the subject's history. In addition, the Investigator shall report on an SAE form all subsequent events or other findings determined to be relevant and shall state for each event or finding whether it is related to study drug. All events determined to be non-serious shall be recorded on the relevant CRF page and entered into clinical database by the CRO or others as agreed in their contractual obligations.

11.2.5.2 Reporting Timelines for Serious Adverse Events and Follow-up Information

Prompt notification of SAEs by the investigator to Mylan is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Mylan has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Mylan will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

In order for Mylan to meet these obligations, the Principal Investigator (or designee) will report to the Mylan any AE classified as serious via telephone, fax, or email within 24 hours of awareness. All available information must be included on the SAE Report form as soon as possible, but in any case no later than 2 calendar days after first knowledge of the SAE. The notification to the Sponsor should be directed to the safety contact [redacted] the Sponsor CRA in parallel. The same timelines apply to reporting of follow-up information.

The Investigator should also be aware of any reporting requirements under his/her responsibility, such as local institutional review boards or ethics committees.

11.2.5.3 Emergency Unblinding

Treatment assignment for an individual subject should be unblinded only in case of a medical/surgical emergency by the investigator, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Treatment should be provided in accordance with the medical condition.

In case of unblinding, the CRO project manager should be contacted by telephone prior to unblinding but no later than 24 hours after unblinding.
If a serious adverse event (SAE) occurred, an SAE Report Form must be completed and forwarded to Mylan's PSRM department. The investigator must document the breaking of the code, and the reasons for doing so on the eCRF, in the site file, and in the medical notes.

The investigator must notify the sponsor in writing as soon as possible following the code break detailing the necessity of the code break. Unblinded information should not be shared with those persons responsible for ongoing conduct of the study such as monitors, statisticians, and other

investigators. The unblinded treatment assignment should only be provided to Mylan PSRM in the event of an SAE, via the SAE report form, for safety reporting to national competent authorities.

11.2.6 Individual Case Management and Periodic Reporting

Individual case management (including expedited reporting) and Development Safety Update Reports (if required) will be managed according to Mylan's internal Standard Operating Procedures and applicable regulatory requirements.

11.2.7 Special Situations

The following situations may be associated with a serious outcome and should be evaluated for expedited reporting to the sponsor.

- Any diagnosis of **Cancer** or **Neoplasm** is to be reported as a serious adverse event.

- **Emergency Room Visits:** Events that result in emergency room visits that do not result in admission to the hospital are not routinely considered to be serious events; however, these events should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically significant] events).

- **Overdose:** Accidental or intentional overdose, should be reported to the sponsor on an expedited basis (Sponsor CRA and safety contact [redacted]'). Subjects should be monitored appropriately by the investigator for latent effects if overdose is confirmed or suspected. Signs and symptoms associated with overdose are to be recorded as adverse events or as serious AEs. If adverse events associated with overdose fulfil any of the serious criteria (as defined in section '**Serious Adverse Event**'), a completed SAE report form is required to be submitted.

- Reports of **Drug-drug Interaction and Drug Abuse and Medication Errors**: drug interactions or abuse of the study medication must be recorded as AEs. Medication errors will be captured as protocol deviations while any associated signs or symptoms must be recorded as AEs on the CRF. In addition, any serious consequence of drug interactions, drug abuse, or medication error must be reported immediately if these fulfil any of the SAE criteria.

11.3 Exposure to Study Drug During Pregnancy

Any pregnancy occurring while the subject is on study drug or within 28 days of the subject's last dose must be reported to Mylan PSRM within 24 hours of awareness.

While pregnancy itself (or positive pregnancy test) is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons (e.g. medical or surgical management of ectopic pregnancy) will be recorded as an AE or a SAE. Any SAE involving the

mother or fetus must also be reported via the SAE Report Form. Miscarriage, congenital anomaly, neonatal death, and infant death are serious adverse events.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered to be an elective procedure and not an adverse event; nevertheless, Mylan requests that the outcome (e.g. elective termination) be reported within 24 hours and sent as a follow-up on the Mylan Delivery and Infant Follow-up Form.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. Male subjects will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or 28 days after the subject's discontinuation visit. Partner pregnancies are to be reported on the Pregnancy Report form after consent of the pregnant female is obtained.
Pregnancy updates are to be submitted to Mylan [redacted] at least every 3-months until birth or termination using the Pregnancy Report/Delivery and Infant Follow-up Form.

12 STATISTICAL STATEMENT AND CONSIDERATIONS

Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock. The SAP will include detailed statistical aspects of the efficacy and safety analysis.

12.1 Significance Level

Statistical tests will be conducted at the 5% significance level unless otherwise indicated.

12.2 Analysis Populations

Three analysis populations are defined as follows:

12.2.1 Safety Population

The safety population includes all randomized subjects who received study treatment.

12.2.2 Modified Intent to Treat (mITT)

1. The mITT population includes all randomized subjects who met the inclusion/exclusion criteria, received study treatment, and returned for at least one post-base line visit.
2. The mITT population will be used to compare both test and reference products to placebo for the superiority analysis.
3. Subjects discontinued early for other reasons included in the mITT population, using Last Observation Carried Forward (LOCF).

12.2.3 Per-Protocol Population (PP)

The per-protocol population (PP) includes
1. The per-protocol population will be the definitive population for equivalence analysis.

2. All randomized subjects who meet all the inclusion/exclusion criteria.
3. Completed study in compliance with the protocol.
4. Administered a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study.
5. Returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) OR discontinued from the study as a treatment failure.
6. Subjects discontinued early from the study due to lack of treatment effect should be included in the PP population, using Last Observation Carried Forward (LOCF).

12.3 Efficacy Analysis

1. The primary endpoint of the study is Mean change in the total WOMAC pain subscale score for the target knee, from baseline to week 4 in Section 8.1 of this protocol.

2. All Efficacy analyses will be performed on the per-protocol and mITT populations. PP population will be definitive for equivalence analysis and mITT population will be definitive for superiority analysis.

12.3.1 Equivalence test between Test Drug and reference product

Bioequivalence will be established for the primary endpoint (WOMAC® pain Score) if the 90% confidence interval for the test/reference ratio of mean change from baseline to week 4 is contained within [0.80, 1.25], using the per-protocol population.
The compound hypothesis to test is:
H_0: $\mu T / \mu R \leq \theta_1$ or $\mu T / \mu R \geq \theta_2$ versus H_A : $\theta_1 < \mu T / \mu R < \theta_2$
Where μT = mean of test treatment, and μR = mean of reference treatment.
H_0 will be rejected with a type I error $\alpha = 0.05$ (two 1-sided tests), if the 90% confidence interval for the ratio of means between test and reference products ($\mu T / \mu R$) is contained within the interval [θ_1, θ_2], where $\theta_1 = 0.80$ and $\theta_2 = 1.25$.
Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

12.3.2 Superiority test between Test Drug and placebo & superiority test between reference product and placebo

As a parameter for determining adequate study sensitivity, the Test Drugand RLD should both be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint (mean change from baseline), using the mITT study population and last observation carried forward (LOCF).

H_0: μT or $\mu R \geq \mu$Placebo versus H_A :μT or $\mu R < \mu$Placebo
Where μT = mean of test treatment, and μR = mean of reference treatment.

H_0 will be rejected with a type I error $\alpha = 0.05$ (2-sided test). Rejection of the null hypothesis H_0 supports the conclusion of superiority to placebo. Analysis of covariance (ANCOVA) will be used to

compare Test Drugto placebo and RLD to placebo separately. The model will consist of treatment, investigator and baseline value as covariate. Post hoc test comparison will be made to detect the group difference.

12.3.3 Analysis of Secondary Efficacy Endpoint

1. Mean change in the total WOMAC pain subscale score for the target knee, from baseline to week 2.
2. Mean change in the WOMAC pain subscale score at week 4 for subgroup subjects whose baseline WOMAC pain score less than or equal to 10.
3. Mean change in pain on movement (POM) after 100 meter walk on a Visual Analog Scale (VAS) for target knee from baseline to week 4
4. Average number of days of acetaminophen (paracetamol)consumption during the trial
5. Average dose of acetaminophen (paracetamol)during the trial

For subgroup analysis, similar method as primary analysis will be performed for equivalence and superiority tests. For other secondary endpoints, analysis of covariance (ANCOVA) will be used to compare Test Drugto placebo and RLD to placebo separately. The model will consist of treatment, center and baseline value as covariate. Average duration and dosage of acetaminophen (paracetamol) consumption during the trial will be summarized by descriptive statistics.

12.4 Safety Analysis

All safety analyses will be performed on safety population.

Safety data will be summarized for the safety population by treatment group. Summary statistics (for example: n, mean, minimum, and maximum) will be included for continuous variables. Summarizations of categorical variables will be presented in tabular form (n and percentages). Safety of drug regimen will be assessed for treatment-emergent AEs and SAEs. Vital signs, clinical laboratory evaluations, pregnancy test, physical examinations, and ECG recordings may be performed for screening and safety monitoring, but will not be used to assess comparative safety. Clinically significant changes from baseline for clinical laboratory tests, vital signs, ECGs, and changes in physical examination results will be recorded as adverse events.

Adverse events will be classified by the primary MedDRA System Organ Class, MedDRA Preferred Term, and the investigator's assessment of the relationship of the adverse event to the study medication. The analysis will be conducted on the safety population.

Safety Endpoints:

1. The incidence of treatment-emergent adverse events.
2. Application site reaction evaluation

Vital Signs and Physical Examination

Descriptive statistics of vital parameters and physical examinations at each visit (except at the start of run-in period visit) for each treatment group will be provided.

Laboratory Investigations

Descriptive statistics of each laboratory parameter investigated during the course of the study will be provided for each treatment group.

12.5 Demographic and Baseline Characteristics

Demographic characteristics and baseline Characteristics will be summarized by treatment, subject disposition, reasons for withdrawal or by any other variables as appropriate .All continuous variables will be represented by n, mean, standard deviation, minimum, median and maximum and All the categorical variables will be presented as counts and percentages.

12.6 Sample Size Considerations

Equivalence between test and reference product[7]

At least 261 subjects in Test Drugand 261 subjects in Reference product will be required to show bioequivalence between Test and Reference product with 90% power and 5% level of significance assuming below estimates:

1) 5% difference between Test and Reference of mean change in WOMAC score
2) 75 % Inter subject coefficient of variation for Reference in WOMAC Score
3) Equivalence margin of 80.00-125.00%

Superiority of test and reference product over placebo

At least 363 number of subjects will be required in each arm to prove the superiority of test/ reference product and placebo product with 90% power and 5% level of significance.

Considering 10% dropout rate, around 1212 subjects would be required to enroll for the study. All Subjects would be randomize in 1:1:1 treatment allocation.

Conclusion: Since the study has two hypotheses viz Equivalence and Superiority, we have chosen the highest sample size.

Test Product: 404 subjects.

Reference Product: 404 subjects

Placebo: 404 subjects

13 ETHICAL REQUIREMENTS

Sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

13.1 Informed Consent

The principles of Informed Consent, according to International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP) will be followed. A copy of the proposed consent form must be submitted to the IEC/IRB, together with the protocol, for approval.

Subjects must provide written informed consent prior to any study procedures being completed. The investigator is responsible for obtaining informed consent, signed by each subject prior to entry into the study. Each subject's signed informed consent must be kept on file by the investigator for Regulatory Authorities' inspection at any time. A copy of the signed consent form will be given to the subject or subject's legally acceptable representative (LAR) & Impartial Witness (IW), if applicable. A notation will be made in the subject's medical record indicating the date informed consent was obtained.

13.2 Independent Ethics Committee/Institutional review Board

The study and the patient informed consent form must be approved in writing by an appropriate IEC/ IRB prior to enrollment of any study subjects.

Any changes to the protocol as well as a change of investigator, which is approved by the sponsor, must also be approved by the site's IEC/IRB and documentation of this approval provided to the sponsor/designee. Records of the IEC/IRB review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to inspection by Regulatory Authorities during or after completion of the study. SAEs must also be reported to the IEC/IRB (or as applicable).

Periodic status reports must be submitted to the IEC/IRB at least annually, as well as notification of completion or termination of the study. A copy of all reports submitted to the IEC/IRB must be sent to the sponsor/ designee.

The investigator shall ensure that an IEC/IRB shall be responsible for the initial and continuing review and approval of the proposed clinical study.

13.3 Subject Confidentiality

The Subjects Medical records and study data will be kept confidential in compliance with the applicable regulatory guidelines. However, as per the requirements regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the sponsor, it is required that the investigator permit the study monitor, sponsor auditor, and/or regulatory authority representative to review that portion of the subject's medical record that is directly related to the study. This shall

include all study relevant documentation including subject medical histories to verify eligibility and other source documents.

As part of the required content of informed consent, the subjects must be informed that his/her medical chart may be reviewed by the sponsor, the sponsor's and/or regulatory authority's representatives. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

14 DOCUMENTATION

14.1 Maintenance and Retention of Records

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report form, worksheets and other pertinent source documents must be retained in accordance with the applicable requirements of the country where the study is being conducted as well as the country where the study will be submitted.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

14.2 Case Report Forms (CRF)

Data will be documented in the eCRF to capture the trial related data from source document/any other pertinent documents.

SAE reporting by Investigator shall be done as per the regulatory requirements, and any related supporting information and/or documents shall be sent by appropriate mode of communication.

Subjects are not to be identified on eCRFs by name; appropriately coded identification and the subject's initials must be used. The investigator must keep a separate log of the subject's names and addresses.

14.3 Primary Source Documents

The investigator must maintain primary source documents supporting significant data for each subject's medical notes. These documents, which are considered "source data", should include (but not limited to) documentation of:

- Demographic information

- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of adverse events, and changes in medication usage, including the date the study drug commenced and completed.
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible adverse events
- An original, signed informed consent for study participation
- The investigator must also retain all subject specific printouts/reports of tests/procedures performed as a requirement of the study.

14.4 Study Monitoring

The study will be monitored by the assigned monitor in compliance with Good Clinical Practices Guideline and applicable regulations. The investigator will be visited by a monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol, standard operating procedures (SOPs), GCP and applicable regulatory requirements.

The study monitor will review the informed consent forms and verify eCRF entries with the source documents (hospital/clinic records). The monitor will review the maintenance of regulatory documentation, drug accountability, and on a regular basis the progress of the study with the investigator and site personnel. At the end of the study, a closeout monitoring visit will be performed.

The coordinator and/or investigator should be available to answer questions or resolve data discrepancies/clarifications. Adequate time and space for these visits should be made available by the investigator and by the site personnel for the monitoring activities at site.

14.5 Audits and Inspections

During the course of the study and/or after it is going to be completed, one or more site visits may be undertaken by auditors as authorized representatives of the sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with recognized GCP guidelines and laws.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during/after the study and are based on the local and international regulations.

14.6 Modifications to the Protocol

The procedures defined in the protocol will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no deviations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the sponsor and the IEC/IRB prior to implementation.

All amendments to the protocol, which involve substantial changes in study design, procedure, analyses, will be submitted to regulatory authorities for prior approval.

15 CONFIDENTIALITY, USE OF INFORMATION, AND PUBLICATION

All information supplied by the sponsor in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e. the clinical protocol, case report forms), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by the sponsor in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to any unauthorized person or use in any unauthorized manner without written consent of the sponsor, and shall not be used except in the performance of the study.

The information developed during the course of this clinical study is also considered confidential, and will be used by the sponsor in connection with the development of the drug. The information may be disclosed as deemed necessary by the sponsor. To allow the use of the information derived from this clinical study, the investigator is obliged to provide the sponsor with complete test results and all data developed in the study.

The investigator shall not make any publication related to this study without the express written permission of the sponsor.

16 FURTHER REQUIREMENTS AND GENERAL INFORMATION

16.1 Contract Research Organization for Clinical Operations

CRO will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, management of SAE reports, and data management. Before subjects are

screened at each study site, the study monitor will review study responsibilities with the investigators and other study site staff, as appropriate.

16.2 Clinical Data Management

Data Management will be performed by the sponsor's designated facility. Data entry screens will be designed to look like paper forms for data entry. User Acceptance Testing will be performed before making the study live for data entry. Once data entry is completed, activities like data validation, quality review, medical coding, database lock and datasets export etc. will be performed. All adverse events will be coded using the current version of MedDRA and concomitant medications will be coded using the current version of WHO DD (WHO Drug Dictionary). Further scope of Data Management activities will be explained in the study specific Data Management Plan and will be approved by the sponsor.

16.3 Ethics Committee Notification of Study Completion or Termination

The Regulatory Authority and the IRB/IEC in each country must be notified within 90 days of completion of the study or within 15 days if the study is terminated early or as per applicable regulatory requirements.

16.4 Insurance

The study will be covered with an appropriate insurance contract.

16.5 Study Report Signatory

Sponsor/CRO may designate one of the participating investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by sponsor.

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