Title Page

Protocol Title:	**Phase 2 Multicenter, Double-blind, Randomized, Parallel-Group, Vehicle-Controlled Study to Evaluate the Efficacy, Safety, and Local Tolerability of G001 in Patients with Osteoarthritis (OA) of the Knee**
Protocol Number:	**2020-G001-P2 (ClinicalTrials.gov ID: NCT05007808)**
Protocol Version:	**4.0 (December 7, 2022)**
Compound:	**G001 (Celecoxib Gel 4% for Topical Administration)**
Brief Title:	**Efficacy and Safety of G001 in Patients with Osteoarthritis (OA) of the Knee**
Study Phase:	**Phase 2**
Sponsor Name:	**Buzzz Pharmaceuticals Limited**
Address:	**15 Main Street, Raheny, Dublin 5, Ireland**
Medical Monitor:	**Atalah Haun** **Veristat, LLC** **Telephone: 647-745-8762** **Email: Atalah.Haun@veristat.com**

This study will be carried out in accordance with Good Clinical Practice (GCP) as set out by the International Council for Harmonisation (ICH).

Protocol Approval Page

Phase 2 Multicenter, Double-blind, Randomized, Parallel-Group, Vehicle-Controlled Study to Evaluate the Efficacy, Safety, and Local Tolerability of G001 in Patients with Osteoarthritis (OA) of the Knee

Protocol Number: 2020-G001-P2

Version: 4.0 (December 7, 2022)

Replaces Version: 3.0 (April 29, 2021)

Buzzz Pharmaceuticals Limited
15 Main Street
Raheny, Dublin 5
Ireland

Sponsor Representatives:

Dr. Anna Power, CEO Buzzz Pharmaceuticals Limited	Date (MMM-DD-YYYY)
Dr. Deirdre O'Keeffe, Head of IP and Portfolio Management Buzzz Pharmaceuticals Limited	Date (MMM-DD-YYYY)

Investigator Signature Page

Phase 2 Multicenter, Double-blind, Randomized, Parallel-Group, Vehicle-Controlled Study to Evaluate the Efficacy, Safety, and Local Tolerability of G001 in Patients with Osteoarthritis (OA) of the Knee

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I have read the protocol and agree to comply with all of the procedures contained herein.

[Name] Principal Investigator	Date (MMM-DD-YYYY)

Table of Contents

List of Abbreviations

ACR	American College of Rheumatology
AE	adverse event
Ae_{24}	urinary excretion over 24 hours
Ae_{48}	urinary excretion over 48 hours
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
AUC_{24}	area under the (analyte concentration versus time) curve from time zero to 24 hours
AUC_{inf}	area under the (analyte concentration versus time) curve from time zero to infinity
AUC_t	area under the (analyte concentration versus time) curve calculated for the interval from time zero to the last measurable time point
BARL	Bay Area Research Logistics
BMI	Body Mass Index
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass surgery
CBC	complete blood count
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
C_{av}	average plasma concentration ($AUC_{24}/24$)
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	apparent total body clearance of drug after topical application ($CL=Dose/AUC_{inf}$)
CLSA	Canadian Longitudinal Study on Aging
C_{max}	maximum measured plasma analyte concentration over the sampling period
C_{min}	minimum/last measured plasma analyte concentration over the sampling period
CONSORT	Consolidated Standards of Reporting Trials
COX	cyclooxygenase
COVID-19	Coronavirus 2019
CRO	Contract Research Organization
CS	clinically significant
CSR	clinical study report
CTA	Clinical Trial Application
CV	coefficient of variation
DBP	diastolic blood pressure
DMC	data monitoring committee
e.g.	*exempli gratia* (for example)
ECG	electrocardiogram

eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	Estimated Glomerular Filtration Rate
EOT	End-of-Treatment (visit)
EOS	End-of-Study (visit)
ES	effect size
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FPFV	first patient first visit
FV1	Flare Visit #1 (Baseline)
FV2	Flare Visit #2 (3-7 days after the last study drug application)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IMP	investigational medicinal product
INR	(prothrombin) International Normalized Ratio
IRB	Institutional Review Board
IWRS	interactive web response system
JRA	Juvenile Rheumatoid Arthritis
JSN	joint space narrowing
K_{el}	apparent first-order elimination rate constant
KLRG	Kellgren and Lawrence Radiographic Grading
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LPLV	last patient last visit
MCID	minimally clinically important difference
MD	mean difference
mg	milligram
MedDRA	Medical Dictionary for Regulatory Activities
MIS	mean irritation score
mITT	modified Intent-to-Treat (Population)
mL	milliliter
MOST	Multicenter Osteoarthritis Study
NHIS	National Health Interview Survey
NIMP	non-investigational medicinal product
NRS	Numerical Rating Scale

NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PGA	Patient Global Assessment
PK	pharmacokinetic
PP	Per Protocol (Population)
QTL	quality tolerance limits
RA	rheumatoid arthritis
RBC	red blood cell
RCT	randomized controlled trial
RF	rheumatoid factor
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SF	synovial fluid
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMD	standardized mean difference
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reactions
$T_{1/2}$	apparent elimination half-life
TEAE	treatment-emergent adverse events
T_{max}	time of the maximum measured plasma analyte concentration over the sampling period
ULN	upper limit of normal
U.S./USA	United States of America
VAS	Visual Analogue Scale
WBC	white blood cell
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
YLD	years lived with disability

Administrative Structure

STUDY FUNCTION	RESPONSIBLE PARTY
Study Sponsor	**Buzzz Pharmaceuticals Limited** 15 Main Street, Raheny, Dublin 5, Ireland Tel: +44-773-310-4786 ***Contact: Dr. Deirdre O'Keeffe*** *Head of IP and Portfolio Management* E-mail: deirdre@hotmail.co.uk
Investigational Medicinal Product (IMP) Manufacturing	**Egis Pharmaceuticals PLC** 1106 Budapest, Keresztúri street 30-38, Hungary Tel: +36-1-803-5555 Fax: +36-1-803-5529, +36-1-803-5511
IMP Labeling & Distribution to Sites	**Bay Area Research Logistics (a division of Bay Area Health Trustee Corp.)** 293 Wellington St. N Unit 123 Hamilton, Ontario, L8L 8E7 Canada Tel: +1-905-527-1938 Tel: +1-844-892-BARL(2275)
Medical Monitor	**Dr. Atalah Haun** Veristat, LLC Tel: +1-647-745-8762 Email: Atalah.Haun@veristat.com
Safety Reporting	**PV and Safety Manager** Veristat, LLC Tel: 1-888-662-0657 Fax: 1-888-662-0647 Email: pharmacovigilance@veristat.com
Clinical Monitoring & Site Management Data Management & Statistical Support	**Veristat, LLC** 134 Turnpike Road, Suite 200 Southborough, MA 01772, USA Tel: +1 508-826-9015 1 Eva Road, Suite 111 Etobicoke, Ontario, M9C 4Z5, Canada ***Contact: Heather Karabaich, Senior Project Manager*** E-mail: Heather.Karabaich@veristat.com
Central Laboratory: Safety laboratory testing	**DYNACARE** 115 Midair Court, Brampton Ontario, L6T 5M3, Canada Tel: + 1-800-668-2714 E-mail: coopera@dynacare.ca

1. Protocol Summary

1.1. Synopsis

Study Title	**Phase 2 Multicenter, Double-blind, Randomized, Parallel-Group, Vehicle-Controlled Study to Evaluate the Efficacy, Safety, and Local Tolerability of G001 in Patients with Osteoarthritis (OA) of the Knee**
Study Design	Double-blind, randomized, parallel-group, vehicle-controlled clinical trial
No. of sites	The study will be completed at approximately 10 centres located in Canada (Quebec and Ontario)
Objectives:	The objectives of this study are to explore the efficacy, safety, and local tolerability of G001 compared to vehicle in patients with symptomatic osteoarthritis (OA) of the knee
Number of Patients	A total of 210 patients are planned to be enrolled to provide 174 evaluable patients (i.e. the modified intent-to-treat [mITT] population for the primary efficacy analysis)
Study Population	Adult patients with primary OA of the knee and moderate OA pain at the time of enrolment
Inclusion Criteria	Patients must meet all of the following criteria to qualify for the study: 1. Male or female age ≥40 years 2. Documented diagnosis of OA of the knee, meeting American College of Rheumatology (ACR) criteria for classification of idiopathic (primary) OA (see Appendix 1) for at least 6 months prior to Screening 3. Radiologic evidence of OA of the knee of grade 2 (mild) or grade 3 (moderate) according to Kellgren and Lawrence Radiographic Grading (see Appendix 2) 4. Worst daily pain (within 24 hours prior to Screening and Baseline) in the index knee between 4 and 8 on the 11-point pain Numerical Rating Scale (NRS) 5. On stable analgesic therapy (i.e. at least 3 days per week for at least 30 days prior to Screening) with an oral or topical non-steroidal anti-inflammatory drug (NSAID) and/or acetaminophen 6. In reasonably good general health (apart from OA), as assessed by the Investigator 7. Females of childbearing potential: adequate birth control and negative pregnancy test at Screening and Baseline. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 24 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the Investigator (e.g., Müllerian agenesis). Adequate birth control is defined as: stable dose of an oral contraceptive for at least 2 months prior to the first study drug administration, intrauterine device, bilateral tubal ligation, barrier method of contraception in conjunction with spermicidal jelly, or abstinence.

	8. Negative urine drug screen (including for cannabinoids) at Screening and Baseline 9. Subject is willing to participate in the study, comply with the study requirements and voluntarily provide written informed consent. ***Additional Inclusion Criteria Assessed at Baseline/Flare Visit #1 (FV1):*** Following Screening, prior NSAID and acetaminophen use will be discontinued to allow for washout (3 to 7 days) and symptom flare. Acetaminophen may be used as rescue medication only, with the following exception: no rescue medication is allowed within 12 hours prior to the Baseline/FV1 visit. 10. Development of a flare of pain following washout of stable analgesic (NSAID and/or acetaminophen) therapy, defined as follows: • An increase of ≥2 points (out of possible 20) from the Screening assessment in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale score for the index knee; and • A score of ≥2 points (out of possible 4) on at least one of the 5 items in the WOMAC Pain Subscale (for the index knee).
Exclusion Criteria	Patients who meet any of the following criteria will be excluded from the study: Exclusions Related to OA: 1. Radiologic evidence of severe OA of the knee (Kellgren and Lawrence grade 4) (see Appendix 2) 2. Secondary OA of the index knee (such as septic arthritis, inflammatory joint disease, gout, articular fracture, major dysplasia, congenital abnormality, hemochromatosis) 3. Any other arthritis, included but not limited to rheumatoid arthritis (RA), psoriatic arthritis, etc. 4. History of pseudo-gout or inflammatory flare-ups 5. History of severe neurological conditions (such as multiple sclerosis, sciatica, fibromyalgia, etc.) 6. Any other chronic pain conditions (e.g., back pain) or disabling conditions affecting the joints 7. Non-ambulatory or requires the use of crutches or a walker 8. Started using a cane within 30 days prior to Screening 9. Worst daily pain (within 24 hours prior to Baseline/FV1) in the contralateral knee assessed as >2 on the 11-point pain NRS scale. Study Drug-Related Exclusions & Other Medical Conditions 10. Skin disorder present at the study drug application site 11. Presence of contraindications, warnings, or precautions (listed in the Canadian Product Monograph for oral celecoxib), that may put the subject at risk, as assessed by the Investigator 12. Known sensitivity to celecoxib, any NSAID, or menthol 13. History of aspirin-sensitive asthma 14. History of any of the following: a. Known coronary artery disease or cerebral artery disease

	b. Coronary artery bypass surgery (CABG) within 1 year prior to Screening c. Any other severe or uncontrolled cardiovascular disease, as assessed by the Investigator d. Systolic blood pressure (SBP) >149 mmHg and/or diastolic blood pressure (DBP) >94 mmHg at Screening 15. Severe, uncontrolled hepatic, renal, or other systemic disease, as assessed by the Investigator 16. Any malignancy within the previous 5 years, except for superficial skin cancer not on the index knee, cured with local therapy 17. Documented gastroduodenal ulcer or gastrointestinal (GI) bleeding within the last 6 months or presence of other GI disorder that could put the patient at increased risk or interfere with the interpretation of the safety results of the study 18. Uncontrolled diabetes or diabetic neuropathy 19. Psychiatric or psychological conditions that in the opinion of the Investigator may affect the subject's pain assessments (such as depression, anxiety, pain catastrophizing, poor sleep quality) 20. Any of the following abnormal Screening laboratory test results: a. serum creatinine ≥ 1.5 times the upper limit of normal (ULN) or Estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2 (Appendix 7); b. aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma-glutamyl transferase (GGT) ≥ 2 times the ULN; c. hemoglobin < 10 g/dL 21. Positive serology for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody at Screening 22. Documented alcohol or other substance abuse within 1 year 23. Body Mass Index (BMI) above 40 kg/m^2 24. Patients who are currently pregnant or planning to be become pregnant or are breast-feeding. <u>Prohibited Prior, Current, or Planned Treatments:</u> 25. Any history of major surgery to the index knee, or minor knee surgery or injury to the index knee within 1 year prior to Screening 26. Knee arthroscopy (index knee) within 3 months prior to Screening 27. Planned or candidate for knee replacement or knee reconstruction surgery 28. Treatment with or need for any of the following: (1) oral or intramuscular corticosteroids within the past 90 days; (2) intra-articular corticosteroid injection into the index knee within the past 90 days, or into any other joint within the past 30 days; (3) current use of topical corticosteroids on the index knee 29. Received intra-articular viscosupplementation/hyaluronate, joint lavage, or other invasive therapies to the index knee in the past 90 days

	30. Prior stable therapy (defined as >3 days per week prior to the Screening) with an opioid analgesic, or anticipated need for opioid analgesic use during the study 31. Use of sedative hypnotic medication, antidepressants with known analgesic effect, antipsychotics, antiepileptics, and anti-Parkinson drugs within the past 14 days Note: "Known analgesic effect" is defined as any documented evidence of a significant effect on pain outcomes, and is not equivalent to an approved indication or proven efficacy. 32. Regular use of medication for headaches (≥10 days within 30 days prior to Screening) 33. Use of another investigational drug within the previous 30 days or five half-lives of the investigational product, whichever is longer 34. Use of any oral or topical NSAID (apart from the investigational medicinal product [IMP]) is prohibited during the study 35. Receipt of a coronavirus 2019 (COVID-19) vaccine within 7 days prior to Screening, or anticipated during the study (between Screening and Week 5). Patients who received their first dose of the vaccine may be enrolled as long as their second dose is scheduled later than the planned Week 5 study visit. The dates of the first and second COVID-19 vaccine dose (actual or planned) should be documented in the patient's study file. ***Additional Exclusion Criterion Assessed at Baseline/FV1:*** 36. Non-compliance with the daily diary requirement during the 7-day Screening period (defined as <3 days of daily or nightly pain assessments or <3 days of rescue medication entries).
Study duration	Each patient's participation will be approximately 7 weeks (~1 week Screening, 4 weeks of treatment, and 2 weeks of post-treatment follow-up). Additional pre-screening time (after informed consent was obtained) may be required for washout periods and radiological examination.
Study Assessments	Following Screening, prior NSAID and/or acetaminophen use will be discontinued to allow for washout (3 to 7 days) and symptom flare. Acetaminophen may be used as rescue medication only, with the following exception: no rescue medication is allowed within the 12 hours prior to the Screening Visit and the Baseline/FV1 visit. Patients will be given a study diary and instructed to enter the following on a daily basis during the 7-day screening period: • Between 6 a.m. and 7 a.m., patients should rate their night-time pain in the index knee (i.e., knee selected for study treatment) on the 11-point pain NRS • Between 10 p.m. and 11 p.m., patients should rate their worse pain in the index knee during the day and enter any breakthrough pain medication (acetaminophen) use during the day. Diary entries will be reviewed at the Baseline/FV1 visit. Eligible patients with adequate OA pain in the index knee at the Baseline/FV1 visit will be randomly assigned in a 1:1 allocation ratio to receive G001 or Vehicle Gel. Patients will have a demonstration of the study drug application at the clinic and receive their first dose before being sent home. Rescue medication use is

	discouraged, but acetaminophen may be used, as needed, at a dose not exceeding 500 mg per dose and 2,000 mg/day to manage breakthrough pain. No rescue medication use is permitted within 2 hours after each IMP application, and within 12 hours prior to each efficacy assessment (i.e., at the Week 2, Week 4/End-of-Treatment [EOT] visits, and Week 5/Flare Visit #2 [FV2]). Patients will be given a study diary and instructed to enter the following on a daily basis: • Between 6 a.m. and 7 a.m. (before the first daily study drug application), patients should rate their night-time pain in the index (i.e., treated) knee • During the day: patients should enter the time of each study drug application • Between 10 p.m. and 11 p.m. (before the last daily study drug application), patients should rate their worse pain in the index knee during the day and enter any adverse event (AE) experienced, and breakthrough pain medication use during the day. Patients will return to the clinic twice during the treatment period for efficacy and safety assessments: at Week 2 (after 14 ± 1 day of study treatment), and at Week 4/EOT (after 28 ± 2 days of study treatment). During these visits, patients will undergo the following efficacy assessments: WOMAC Index, Patient Global Assessment (PGA), Investigator Global Assessment (IGA), review of patient diary. In addition, the Investigator (or qualified designee) will contact the patient by phone after one week of treatment (Week 1, study Day 8 ± 1), and after three weeks of treatment (Week 3, study Day 22 ± 1), to verify compliance with the study drug application and daily diary completion requirements, and to follow up on how the IMP is tolerated. Patients will return to the clinic 3 to 7 days after the last IMP application for a second Flare Visit (Week 5/FV2), and within approximately 2 weeks after the last IMP application (Week 6; Day 43 ± 3) for an End-of-Study (EOS) evaluation. Daily diary completion will continue (as described above) until the Week 5/FV2 visit. Patients who discontinue study treatment prematurely will be asked to return to the clinic for the EOT visit assessments at the time of withdrawal, and the EOS visit 14 ± 2 days after the last IMP application, unless the patient withdraws consent from any further study participation. Safety will be assessed throughout the study through recording of AEs and concomitant medications, complete physical examination, safety laboratory tests (complete blood count [CBC], blood chemistry, coagulation tests, and urinalysis), 12-lead electrocardiogram (ECG), vital signs, and skin irritation assessments at the following visits: • AEs and concomitant medications: self-reported or solicited by non-directive questioning of the patient at each visit. AEs ongoing at the EOS visit will be followed until resolution or an acceptable outcome has been reached, as assessed by the Medical Monitor. • Safety laboratory tests (including a urine pregnancy test for females of childbearing potential) at Screening, Baseline/FV1, Week 2, Week 4/EOT, and Week 6/EOS. A repeat serum pregnancy test is required in case the urine test is positive. • Standard 12-lead ECGs (in a supine position, after resting for at least 5 minutes) at the Screening, and Week 4/EOT visits.

	• Complete physical examination at Screening and Week 4/EOT, and a symptom-driven examination at Week 6/EOS. • Vital signs: sitting (after 3 minutes of rest) at Screening, Baseline/FV1, Week 2, Week 4/EOT, and Week 6/EOS. • Skin irritation will be tested on a scale of 0 to 7 (from 0=no evidence of irritation to 7=strong reaction spreading beyond test site) at Week 2, Week 4/EOT, and Week 6/EOS.
Primary outcome measure(s)	• Change from Baseline in WOMAC Pain Subscale Score, at Week 4/EOT The WOMAC Pain Subscale score is derived by summing the five pain scores on the WOMAC OA Index (pain during walking, using stairs, in bed, sitting or lying, and standing), each measured on a 5-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe, and 4=extreme). The maximum WOMAC Pain Subscale rating is 20 and higher scores indicate worse pain.
Secondary outcome measures	• Mean worst *daytime* and mean worst *nighttime* pain severity scores (11-point pain NRS, from patient diary) at Week 4/EOT and Week 5/FV2, including mean changes from Baseline • Percentages of patients achieving ≥20%, ≥30%, and ≥50% reduction from Baseline in worst *daytime* pain severity scores (11-point pain NRS, from patient diary) at Week 4/EOT • Percentages of patients achieving ≥20%, ≥30%, and ≥50% reduction from Baseline in worst *nighttime* pain severity scores (11-point pain NRS, from patient diary) at Week 4/EOT • Change from Baseline to Week 4/EOT in WOMAC Physical Function Subscale score • Change from Baseline to Week 4/EOT in WOMAC Total score • Change from Baseline to Week 4/EOT in WOMAC Stiffness Subscale score • Change from Baseline to Week 2 in WOMAC Total and Subscale scores • Change from Week 4/EOT to Week 5/FV2 in WOMAC Total and Subscale scores • Change from Baseline in PGA of disease activity over time • Change from Baseline in IGA of disease activity over time • PGA and IGA of overall treatment benefit at Week 2 and Week 4/EOT • Incidence of rescue medication use, number of doses, and percentage of days with any rescue medication use during the last week of study treatment, and overall during the study treatment period (between the first and last study drug dose dates). The WOMAC OA Index consists of 24 items divided into 3 subscales: Pain (5 items), Stiffness (2 items), and Physical Function (17 items). Each item is measured on a 5-point Likert scale. Scoring instructions are provided in the in the WOMAC® 3.1 User Guide XI. The pain NRS is an ordinal 11-point Likert scale, with scores ranging from 0 (no pain) to 10 (worst possible pain). PGA and IGA of disease activity are the patient's and assessor's evaluation of OA, respectively, in the in the index knee over the last 48 hours on a 5-point Likert scale, where 0=very good; 1=good; 2=fair; 3=poor; and 4=very poor. PGA

	and IGA of treatment benefit use the same scale and time frame, evaluating the impact of the treatment.
Safety outcome measures	• Frequency and severity of AEs, study drug-related AEs, serious adverse events (SAEs), and AEs leading to study drug discontinuation • Changes in safety laboratory test results, vital signs measurements, 12-lead ECG, and physical examination findings. • Frequency and severity of application site AEs • Skin irritation test scores at Week 2, Week 4/EOT, and Week 6/EOS.
Test Product Route and Doses	G001 (Celecoxib Gel 4%) for topical administration, containing celecoxib 40 mg/g as active ingredient. The formulation also includes menthol 1.5% (15 mg/g), added as solubilizer.
Reference Products Route and Doses	Vehicle formulation, containing all excipients of G001 (including menthol 1.5%), but without celecoxib.
Investigational Medicinal Product Application Method, Frequency and Duration of Treatment	4 grams of the IMP (test or reference product) will be applied to the target knee four times daily for 4 weeks as follows: • 1st dose between 6 a.m. and 7 a.m. • 2nd dose: between 11 a.m. and 12 p.m. (~5 hours after the first dose) • 3rd dose: between 4 p.m. and 5 p.m. (~5 hours after the second dose) • 4th dose: between 10 p.m. and 11 p.m. (~6 hours after the third dose and shortly after the daily pain assessment). Note: the first study drug application (Day 1) may occur between 6 a.m. and 8 a.m. Subsequent application times on Day 1 may be modified accordingly, to maintain the ~5-hour interval between consecutive applications. Accurate dosing will be ensured by using a dosing card. The patient will be instructed to measure 4 grams of the gel using the dosing card, then apply the measured amount to the index knee, and massage it in over at least 1 minute to ensure adequate application over the affected joint. The first dose will be applied at the clinic, in the presence of the designated unblinded administrator; subsequent applications will be made by the patient (at the clinic or their home, as applicable). Study treatment will continue for 4 weeks (28 ± 2 days).
Duration of follow-up	Patients will have a safety follow-up assessment 2 weeks (14 ± 3 days) after their last IMP application. Follow-up of SAEs and AE related to the IMP will continue until resolution of the event or until a stable condition is reached.
Statistical Considerations	***Analysis Populations:*** • Modified Intent-to-Treat Population (mITT): The mITT will include all randomized patients who received at least one dose of study drug and provided both Baseline/FV1 and Week 4/EOT efficacy assessments. The mITT population will be the primary analysis population for the assessment of efficacy, with patients assessed according to the treatment they were randomized to. • Per Protocol (PP) Population: The PP population will include all patients in the mITT population who completed the study without major protocol violations that could impact the assessment of efficacy. The primary and

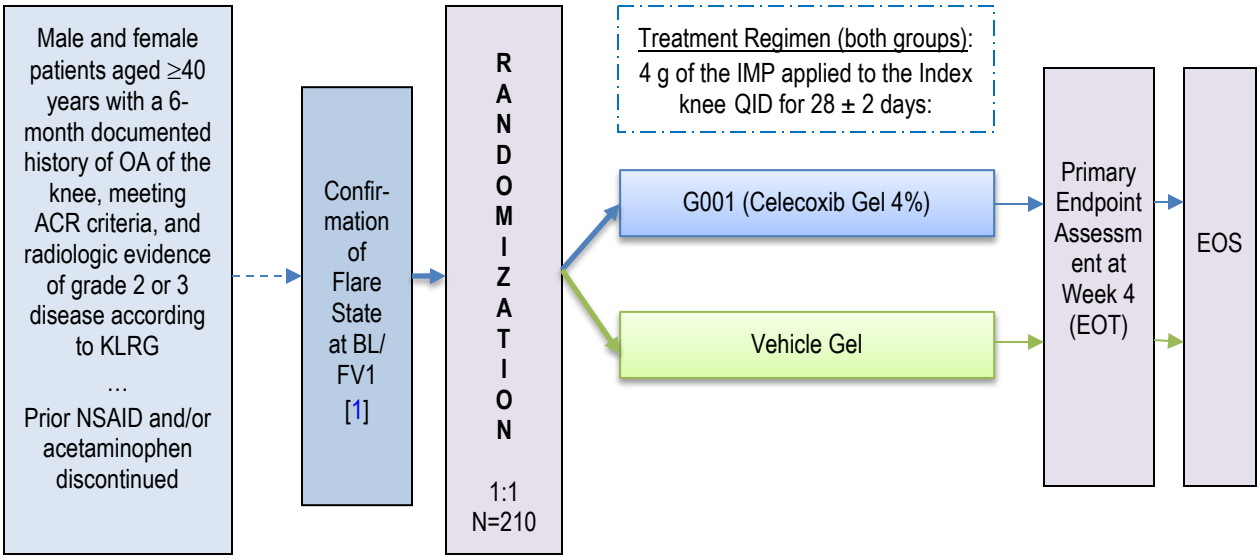
	secondary efficacy analyses will also be completed on the PP population as supportive. • Safety Population: The Safety population will include all patients who received any amount of study drug. Patients will be assessed according to the treatment they received. The Safety Population will be used for all safety analyses. ***Sample Size Estimation:*** A total sample size of 174 evaluable patients (87 per group) achieves 80% power to detect a difference among treatment groups analysed using a t-test with a significance level (alpha) of 0.05. The assumed difference in group means from vehicle control under the alternative hypothesis is 1.5 points in the WOMAC Likert pain subscale (0-20 scale). The common standard deviation (SD) is assumed to be 3.5. Based on available literature, it is estimated that up to 20% of patients may withdraw from the study prior to the Week 4 efficacy assessment. Therefore, to control for possible dropouts, the sample size is increased to 210, or 105 per treatment arm. ***Analysis Methods:*** A detailed Statistical Analysis Plan (SAP) will be developed. All data collected will be documented using summary tables, figures, and/or patient data listings presented by treatment group. For continuous variables, descriptive statistics (number [n], mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. The primary endpoint, change from Baseline in the WOMAC Pain Subscale rating at the Week 4/EOT visit, will be analyzed via an analysis of covariance (ANCOVA) model to compute the t-test for the difference between group means adjusted for Baseline WOMAC pain score. The analysis will be performed on the mITT population with no imputation for missing data. Statistical significance will be assessed using a significance level of 0.05. Changes from baseline in average worst *daytime* and in average worst *nighttime* pain severity scores at Week 4/EOT in the two treatment groups will be compared using a t-test. Percentages of patients achieving ≥20%, ≥30% and ≥50% reduction from baseline in worst *daytime* pain and in worst *nighttime* pain severity scores (11-point pain NRS) at Week 4/EOT will be compared between treatment groups using Fisher's exact test. The analysis of secondary efficacy endpoints of WOMAC Physical Function Subscale, WOMAC Stiffness Subscale and WOMAC Total Score will be consistent with that described for the primary endpoint. For PGA and IGA, patients will be classified according to the following three categories: (1) "improved" (defined as a reduction of 2 grades or more from Baseline for grades 2 through 4 or a change in grade from 1 to 0); (2) "worsened" (defined as an increase of 2 or more grades from Baseline for grades 0 through 2 or a change in grade from 3 to 4); or (3) "no change" (remaining patients). The categorical responses will be presented by treatment and visit.

	Rescue medication (acetaminophen) use will be assessed in terms of number of rescue doses, total daily dose, and the percentage of days with any rescue medication use during the last week of study treatment, and overall during the study treatment period (between the first and last study drug dose dates). Subgroup analyses of primary and select secondary endpoints may be performed on prior OA treatment (pre-study NSAID or acetaminophen use only) depending on the number of patients in each category. **Safety:** Adverse events (AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) and presented by System Organ Class (SOC) and Preferred Term for each treatment group. Additional displays will highlight the Investigator-rated severity and relationship to study treatment as well as SAEs, withdrawals due to AEs, and application site AEs. Laboratory parameters (and changes from Baseline in these parameters) will be summarized. In additional, shift changes in categories (normal, low, high, missing) will be presented by treatment group across the visits. Clinically relevant laboratory abnormalities will be recorded as AEs. Vital signs measurements (and changes from Baseline in these measurements) will be summarized. Clinically relevant changes in vital signs will be recorded as AEs. Clinically relevant abnormal physical examination findings will be recorded as medical history at Baseline (prior to the first dose of study treatment), and as AEs if detected after the first dose of study treatment. Local tolerability (skin irritation) assessments will be summarized by treatment group and study visits.

1.2. Study Design Schema

A study design schema is provided in Figure 1.

Figure 1 Study Design Schema



Abbreviations: ACR=American College of Rheumatology; BL=Baseline; EOS=end-of-study; EOT=end-of-treatment; FV1=Flare Visit #1; IMP=Investigational Medicinal Product; KLRG=Kellgren and Lawrence Radiographic Grading; NSAID=nonsteroidal anti-inflammatory drugs; OA=osteoarthritis; QID=*quarter in die* (four times daily); WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

[1] Flare state is confirmed at the Baseline/FV1 visit (3-7 days after the Screening visit) as follows:

- An increase of ≥2 points (out of possible 20) from the screening assessment in the WOMAC Pain Subscale score for the index knee; and
- A score of ≥2 points (out of possible 4) on at least one of the 5 items in the WOMAC Pain Subscale for the index knee.

1.3. Schedule of Assessments (SoA)

Study Visit	**Screening Visit**	**BL/FV1 Visit**	**Week 1 Phone call**	**Week 2 Visit**	**Week 3 Phone call**	**Week 4/EOT Visit**	**Week 5/FV2 Visit**	**Week 6/EOS Visit**
Study Day	**Day -7 to -3**	**Day 1**	**Day 8±1**	**Day 15±1**	**Day 22±1**	**Day 29±2**	**3-7 Days After EOT**	**Day 43±3**
Written informed consent [a]	X							
Demographic data [b]	X							
Medical and medication history [c]	X							
OA diagnosis (ACR criteria) [d]	X							
Radiological examination [e]	X							
WOMAC Index [f]	X	X		X		X	X	
PGA of disease activity [g]	X	X		X		X	X	
IGA of disease activity [g]	X	X		X		X	X	
PGA of overall treatment benefit [g]				X		X		
IGA of overall treatment benefit [g]				X		X		
Worst daily pain 11-point NRS (24-hour recall), index knee [h]	X	X						
Worst daily pain 11-point NRS (24-hour recall), contralateral knee [i]	X	X						
Physical examination [j]	X					X		X
Height, weight, and BMI	X							
Vital signs measurements [k]	X	X		X		X		X
Standard 12-lead ECG [l]	X					X		
Safety Laboratory Testing [m]	X	X		X		X		X
Urine pregnancy test [n]	X	X				X		X
Urine drug screen	X	X		X		X		X
Review of Inclusion / Exclusion criteria	X	X						
Randomization		X						
Study drug dispensing/reconciliation		X		X		X		
Study drug application (4 times per day) [o]		X	X	X	X	X		
Adverse event recording	X	X	X [p]	X	X [p]	X	X	X
Concomitant medications & therapies	X	X	X [p]	X	X [p]	X	X	X
Skin irritation assessment [q]				X		X		X

Study Visit	**Screening Visit**	**BL/FV1 Visit**	**Week 1 Phone call**	**Week 2 Visit**	**Week 3 Phone call**	**Week 4/EOT Visit**	**Week 5/FV2 Visit**	**Week 6/EOS Visit**
Study Day	**Day -7 to -3**	**Day 1**	**Day 8±1**	**Day 15±1**	**Day 22±1**	**Day 29±2**	**3-7 Days After EOT**	**Day 43±3**
Patient diary completion [r]	*Completed by the patient on a daily basis*							
Review of the Patient Diary [s]		X	X [p]	X	X [p]	X	X	

Abbreviations: ACR=American College of Rheumatology; BL=Baseline; BMI=body mass index; BP=blood pressure; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; FV1=Flare Visit #1; FV2=Flare Visit #2; IGA=Investigator Global Assessment; NRS=Numerical Rating Scale; PGA=Patient Global Assessment; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

[a] Written informed consent is required before performing any study-specific tests or procedures.

[b] Demographics include age, gender, and self-reported race/ethnicity.

[c] Medical history OA history (date of diagnosis, prior treatment), general medical history, surgical history, and reproductive status. Medication history includes pharmacological treatment (oral, parenteral, intra-articular, or topical) used in the past 90 days, with focus on medications used for the management of OA, and prohibited medications; see Section 6.8.1.

[d] Documented diagnosis of OA of the knee, meeting ACR criteria for classification of idiopathic (primary) OA (see Appendix 1) for at least 6 months prior to Screening is required for enrolment.

[e] Patients will undergo conventional radiological (X-ray) examination of the index knee during Screening. Exemptions include patients who: (1) had an X-ray of the index knee completed within 3 months prior to the Screening visit, and (2) received no treatment since that may have altered the radiological findings, including OA grade. Radiologic evidence of OA of the knee of grade 2 (mild) or grade 3 (moderate) according to Kellgren and Lawrence Radiographic Grading (see Appendix 2) is required for enrolment.

[f] Patients will complete the 5-point Likert format of the WOMAC® 3.1 Index; see Appendix 3. To qualify for randomization, all participants need to develop a flare of pain following washout (3-7 days) of stable analgesic (NSAID and/or acetaminophen) therapy, defined as (1) an increase of ≥2 points from Screening in the WOMAC Pain Subscale score for the index knee; and (2) a score of ≥2 points on at least one of the 5 items in the WOMAC Pain Subscale (for the index knee).

[g] PGA/IGA of disease activity (or PGA/IGA of treatment benefit) evaluates OA in the in the index knee over the last 48 hours on a 5-point Likert scale, where 0=very good; 1=good; 2=fair; 3=poor; and 4=very poor.

[h] Worst daily pain (within 24 hours prior to Screening and Baseline/FV1) in the index knee needs to be between 4 and 8 on the 11-point pain NRS for enrolment.

[i] Worst daily pain (within 24 hours prior to Baseline/FV1) in the contralateral knee needs to be ≤2 on the 11-point pain NRS scale for enrolment.

[j] Complete physical examination at Screening and Week 4/EOT, and symptom-driven examination at Week 6/EOS. A complete physical examination will be performed with special attention to the cardiovascular, gastrointestinal, and musculoskeletal systems, as well as skin and subcutaneous tissues. Investigators may use medical judgment to determine the need for evaluating the breast, genital, and anorectal areas at each applicable study visit.

[k] Vital signs measurements will include sitting (after 3 minutes of rest) blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature. Two consecutive BP readings (at least 1 minute apart) will be recorded, and the average of the two readings will be entered in the eCRF.

[l] Standard 12-lead ECG, taken in a supine position, after resting for at least 5 minutes.

[m] Includes: Haematology, Biochemistry, Coagulation tests, Urinalysis; see Appendix 5.

[n] A confirmatory serum pregnancy test must be completed in case the urine test is positive. Patients with a positive pregnancy test during Screening will be excluded from the study. Patients with a positive pregnancy test during the treatment or post-treatment follow-up period will be withdrawn from the study.

[o] The first dose will be applied at the clinic, in the presence of a qualified unblinded treatment administrator; subsequent applications will be completed by the patient at the clinic (on Day 15/Week 2 Visit) or at their home (all other applications). Accurate dosing will be ensured by using a dosing card (to be used for all study drug applications). Patients will be dispensed a two-week supply of study drug (three tubes of 100 grams) on Day 1 (Baseline/FV1) and on Day 15 (Week 2 Visit), and will be asked to return all unused study drug supplies at the next study visit.

[p] The Investigator (or qualified designee) will contact the patient by phone after one week of treatment (Week 1, study Day 8 ± 1), and after three weeks of treatment (Week 3, study Day 22 ± 1), to verify compliance with the study drug application and daily diary completion requirements, and to follow up on how the IMP is tolerated.

[q] Skin irritation will be assessed by the Investigator using the Berger/Bowman Scoring Scale; see Appendix 4. To the extent feasible, the same scorer should complete all three skin irritation assessments (Week 2, Week 4/EOT, and Week 6/EOS) for a patient.

[r] Patients will be given a study diary and instructed to enter the following on a daily basis, from the Screening visit through the Week 5/FV2 visit: (1) Each morning between 6 a.m. and 7 a.m. (before the first daily study drug application on treatment days), patients should rate their worst night-time pain in the index knee on the 11-point pain NRS; (2) Between 10 p.m. and 11 p.m. (before the last daily study drug application on each treatment day), patients should rate their worse daytime pain in the index knee on the 11-point pain NRS and enter any adverse event experienced, and breakthrough pain medication use during the day; (3) In addition, on treatment days, patients should enter the time of each study drug application.

[s] Non-compliance with the daily diary requirement during the Screening period (defined as <3 days of daytime or nighttime pain assessments or <3 days of rescue medication entries) will result in exclusion from the study.

2. Introduction

2.1. Background on the Condition: Osteoarthritis

2.1.1. Epidemiology and Disease Burden

Osteoarthritis (OA) is a degenerative joint disease that is highly prevalent, and a leading cause of disability around the globe (Cross *et al.* 2014; GBD 2017). The global incidence and prevalence of OA have been estimated at 14.7 million and 301.6 million, respectively, and the years lived with disability (YLD) associated with OA at 16.3 million (ranking 12th among 328 diseases), with a 31.5% increase in the number of cases, and a 2.4% increase in the age-standardized rates between 2006 and 2016 (GBD 2017; Kolasinski *et al.* 2020). In Canada (as in Western Europe overall), OA is the 10th leading cause of disabilities (GBD 2017).

The estimated national prevalence and incidence rates for OA vary depending on the definition of OA, the specific joint(s) being evaluated, and the population being studied (Vina and Kwoh 2018). Based on data from the National Health Interview Survey (NHIS) collected during 2013–2015, an estimated 54.4 million (22.7%) adults had physician-diagnosed arthritis in the United States (U.S.), and 23.7 million (43.5% of those with arthritis) had arthritis-attributable activity limitations (Barbour et al. 2017; CDC 2020). Of all arthritis cases, over 32.5 million U.S. adults have OA (CDC 2020). In Canada, the overall prevalence of diagnosed OA in primary care is estimated at 14% (Birtwhistle *et al.* 2015). However, a recent report from the Canadian Longitudinal Study on Aging (CLSA) involving 23,186 respondents aged 45 to 85 years indicates that ~21% of this age group has a diagnosis of OA in Canada, and ~25% reported symptoms typical of OA, but without an OA diagnosis (of the ~25%, symptoms were present in one joint in 21%, and in more than one joint in 4.5% of cases). Factors associated with significantly higher likelihood of a diagnosed OA or possible OA included older age, female sex, being overweight or obese, having a greater number of co-occurring conditions, and lower household income (Yip *et al.* 2020). Other recognized person-level risk factors include African-American race, genetic predispositions, diet-related factors, and high bone density/mass, whereas joint-level risk factors include specific bone/joint shapes, thigh flexor muscle weakness, joint malalignment, participation in certain occupational/sports activities, and joint injury (Vina and Kwoh 2018).

Clinically, the knee is the most common site of OA (accounting for approximately 85% of the OA burden worldwide), followed by the hand and hip (Hunter and Bierma-Zeinstra, 2019).

2.1.2. Pathophysiology

Osteoarthritis is a heterogeneous disease with a very complex pathology that involves mechanical, inflammatory, and metabolic factors, which ultimately lead to structural destruction and failure of the synovial joint. Each of the common OA risk factors might instigate a different mechanistic pathway leading to OA. The disease affects the whole joint, and involves cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function. Overall, the disease is an active dynamic alteration arising from an imbalance between the repair and destruction of joint tissues (Vina and Kwoh 2018; Hunter and Bierma-Zeinstra, 2019; Kolasinski *et al.* 2020).

Pain is the most disabling symptom in OA, and a major driver of clinical decision making and health service use. The pain in knee OA is typically an intermittent and mainly weight-bearing (mechanical) pain. Pain mechanisms involved in OA include peripheral nociceptive pain mechanisms, as well as pain sensitization by means of neuropathic pain mechanisms or central pain mechanisms. The concept and understanding of 'flare-ups' in knee OA are evolving; however, they are now considered broader than just an exacerbation of pain (Hunter and Bierma-Zeinstra, 2019).

Clinical diagnosis is made based on symptoms (pain, brief morning stiffness, and functional limitations) and a brief physical examination (crepitus, restricted or painful movement, joint tenderness, and bony enlargement), according to appropriate diagnostic criteria, such as the those from the American College of Rheumatology (ACR) (Altman *et al*. 1986; Kolasinski *et al.* 2020).

2.1.3. Management

The main objectives in the management of knee OA are to alleviate pain, restore function, slow down the progression of disease and maintain a patients' health-related quality of life (Huang *et al.* 2020). According to current treatment guidelines (Bannuru *et al.* 2019; Bruyère *et al.* 2019; Kolasinski *et al.* 2020), a comprehensive plan for the management of OA in an individual patient may include pharmacological treatment (topical, oral, intra-articular), as well as educational, behavioral, psychosocial, and physical interventions. Of the pharmacological interventions, medications with the least systemic exposure (i.e., local therapy) are preferred. Strongly recommended medications for the treatment of knee OA include topical nonsteroidal anti-inflammatory drugs (NSAIDs) as first choice (to be considered prior to use of oral NSAIDs, particularly in patients with more limited disease), oral NSAIDs, and IA glucocorticoid injections, whereas topical capsaicin, acetaminophen, duloxetine, and tramadol are conditionally recommended (Bannuru *et al.* 2019; Kolasinski *et al.* 2020). For oral NSAIDs (the mainstay of the pharmacologic management of OA), doses should be as low as possible, and treatment should be continued for as short a time as possible (Kolasinski *et al.* 2020).

Topical NSAIDs have a moderate effect on pain, with efficacy similar to that of oral NSAIDs; however, due to the low systemic absorption, they have a much better safety profile (Rannou *et al.* 2016). A meta-analysis of 215 randomized controlled trials (RCTs) (41,392 participants) found that the overall treatment effect for pain was the largest with topical NSAIDs (effect size [ES]=1.37, 95% CI 1.19 to 1.55), of which 0.85 (95% CI 0.77 to 0.93) was attributable to contextual effect (i.e., ES of the placebo group) (Zou et al. 2016). The most common adverse events (AEs) associated with topical NSAIDs are local skin reactions, which are minor, and transient (Bannuru *et al.* 2019).

2.2. Background on Oral Celecoxib

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide), a cyclooxygenase (COX)-2 selective inhibitor, belongs to the pharmacological class of NSAIDs. Celecoxib has established analgesic, anti-inflammatory, and antipyretic properties.

Celecoxib capsules for oral use are indicated (in the U.S. and Canada) for relief of symptoms associated with OA, adult rheumatoid arthritis (RA), and ankylosing spondylitis (Celebrex CPM 2022; Celebrex USPI 2021). Additional approved indications include the short-term (≤7 days)

management of moderate to severe acute pain in adults (in conditions such as musculoskeletal and/or soft tissue trauma including sprains, postoperative orthopedic, and pain following dental extraction) in Canada (Celebrex CPM 2022), and Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older, and primary dysmenorrhea in the U.S. (Celebrex USPI 2021). The recommended (and maximum) daily oral dose is 200 mg administered as a single dose or as two divided doses (100 mg twice per day) (Celebrex CPM 2022; Celebrex USPI 2021).

2.2.1. Clinical Experience with Oral Celecoxib

The clinical efficacy of oral celecoxib in the treatment of the signs and symptoms of OA have been demonstrated in placebo- and active-controlled clinical trials of up to 12 weeks duration (Celebrex CPM 2022; Celebrex USPI 2021). Approval for the OA indication was granted based on five pivotal RCTs, including three 12-week placebo- and active (naproxen)-controlled studies (Study C-020, N=1092, Study C-021, N=1214, and Study C-054, N=1060), and two 6-week placebo-controlled studies (Study C-060, N=684, and Study C-087, N=715), as well as five supportive RCTs (FDA Statistical Review 1998; Moore et al. 2005). In patients with OA, treatment with celecoxib 100 mg twice daily or 200 mg once daily resulted in improvement in Western Ontario and McMaster Universities (WOMAC) OA index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, celecoxib doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24 to 48 hours of initiation of dosing. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily (Celebrex CPM 2022; Celebrex USPI 2021). A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily (Williams *et al.* 2000; Williams *et al.* 2001; Celebrex CPM 2022; Celebrex USPI 2021). Response to oral celecoxib was independent of age, gender, severity, or duration of OA (Celebrex CPM 2022).

Significant pain reductions as measured on the Likert version of WOMAC Pain Subscale were also demonstrated in short-term (6-week) randomized, placebo-controlled trials, with mean treatment differences (oral celecoxib compared vs placebo) generally around -1.5 to -1.6 (Williams *et al.* 2000; McKenna *et al.* 2001; Rother *et al.* 2007), and occasionally higher (Gibovsky *et al.* 2003; Essex *et al.* 2014).

A systematic review and meta-analysis of 36 published RCTs involving 17,206 adult patients with OA of the knee(s) or hip(s) (9402 exposed to celecoxib 200 mg/day) found that oral celecoxib was statistically significantly superior to placebo in reducing pain, as assessed by the WOMAC visual analogue scale (VAS) Pain Subscale score at 6 weeks (mean difference [MD] -3.28, 95% CI -4.51 to -2.06, $P < 0.001$; 12 studies, 4178 participants); 12 weeks (standardized mean difference [SMD] -0.32; 95%CI -0.40 to -0.23, $P < 0.001$; 9 studies, 3328 participants); 13 weeks (MD -1.06, 95% CI -1.31 to -0.80, $P < 0.001$; 5 studies, 3853 participants); and 24 weeks (MD -13.1, 95%CI -24.69 to -1.51, $P = 0.03$; 1 study, 631 participants) (Puljak *et al.* 2017).

A detailed description of the chemistry, pharmacology, efficacy, and safety of oral celecoxib is provided in the Celebrex Product Monograph (Celebrex CPM 2022).

2.3. Background on G001 (Celecoxib Gel 4% for Topical Administration)

G001 is a novel gel formulation of celecoxib for topical administration being developed by Buzzz Pharmaceuticals Ltd., Ireland (hereunder referred to as Buzzz or Sponsor) for the treatment of signs and symptoms of OA of the knee and hand.

The following sections provide a brief overview of the nonclinical and clinical experience with G001. Further details, including a description of the chemistry and pharmacology of the product, is provided in the G001 Investigator's Brochure (G001 IB, 2022).

2.3.1. Nonclinical Experience with G001

Data generated in nonclinical models suggest topical application of celecoxib in a gel formulation is effective and well tolerated. In a 5-day study in a rat model of RA, described in the literature, topically administered celecoxib (1%) in two different gel formulations reduced signs of arthritis (arthritis index, dermatological sum score, histopathology) compared to control (Nirbhavane *et al.* 2018). In another study, topical administration of 8% celecoxib gel significantly reduced pain scores at 24.5 and 30.5 hours in a sodium urate model of joint inflammation in Beagle dogs, although there was no effect on edema by this route (Baranowski *et al.* 2018). The average concentrations of celecoxib were similar in the serum and synovial fluid (220.9±92.7 ng/mL and 203.0±0.3 ng/mL, respectively) in a Beagle dog study following 7 days of topical administration. After a 7-day washout, concentrations decreased, but not significantly, suggesting slow clearance of celecoxib.

The Sponsor conducted additional nonclinical toxicology studies to support the clinical study for the celecoxib gel formulation. In *in vitro* local tolerance studies, G001 at concentrations of 3% and 4% showed no evidence of eye hazard in isolated bovine corneas. In *in vivo* local tolerance studies, G001 4% topical gel showed no sensitization effects following repeat administration in albino guinea pigs. Additionally, there were no adverse clinical signs, changes in body weight or food consumption, or signs of skin irritation following 10- or 28-day administration (4 doses per day) in Göttingen minipigs.

2.3.2. Clinical Experience with G001

One double-blind, randomized, parallel-group, single- and multiple-dose study (Study 2019-4679) evaluated the clinical safety, tolerability, and pharmacokinetics (PK) of Celecoxib Gel 1.5% and 4% under single- and multiple dose conditions in healthy volunteers. The study was completed in two consecutive parts.

2.3.2.1. Study 2019-4679 Design and Assessments

In Part I, 18 adult male and female subjects were randomized to receive a single application of the investigational medicinal product (IMP; Celecoxib Gel 1.5% [Treatment A] or Celecoxib Gel 4% [Treatment B]); see Table 1. Concentrations of celecoxib were measured in plasma from PK blood samples collected over a 168-hour interval following IMP application and from urine samples collected over a 48-hour interval postdose. Using these data, maximum measured plasma analyte concentration (C_{max}), area under the concentration versus time curve for the interval from time zero to the last measurable time point (AUC_t), AUC from time zero to infinity (AUC_{inf}), time of the maximum measured plasma analyte concentration (T_{max}), apparent first-order elimination rate

constant (K_{el}), elimination half-life ($T_{1/2}$), urinary excretion over 48 hours (A_{e48}), and percent drug recovered were estimated using a noncompartmental approach.

Upon conclusion of Part I, an interim review of the PK and safety data was completed by the study data monitoring committee (DMC).

Part II was conducted in two cohorts, each consisting of 24 male and female subjects. The treatment schedule for the two cohorts is detailed in Table 1. For both cohorts, PK blood samples were collected over a 24-hour interval on days 1 and 7, and one sample was taken on each of the following study days: 5, 6, 10, 14, 21, 28, and 35. Last measured plasma analyte concentration (C_{min}), C_{max}, AUC from time zero to 24 hours (AUC_{24}), average plasma concentration (C_{av}), T_{max}, fluctuation, urinary excretion over 24 hours (Ae_{24}), and percent drug recovered were estimated using a noncompartmental approach for day 1 and day 7. Ae_{24} was determined based on urine samples collected up to 24 hours following the first drug application on days 1 and 7.

Table 1 G001 Treatment Regimens in Phase 1 Study 2019-4679

Study Part	Cohort	Treatment Group	Dosing Regimen
Part I Single-dose	N/A	Treatment A	Single application of 4 ± 0.10 g of Celecoxib Gel 1.5% to each knee (total of ~8 g containing 120 mg of celecoxib)
		Treatment B	Single application of 4 ± 0.10 g of Celecoxib Gel 4% to each knee (total of ~8 g containing 320 mg of celecoxib)
Part II Multiple-dose	Cohort 1	Treatment C	4 daily applications of 4 ± 0.10 g of Celecoxib Gel 1.5% to the left knee (total of ~16 g containing 240 mg of celecoxib daily) for 7 days
		Treatment D	4 daily applications of 4 ± 0.10 g of Celecoxib Gel 4% to the left knee (total of ~16 g containing 640 mg of celecoxib daily) for 7 days
	Cohort 2	Treatment E	4 daily applications of 4 ± 0.10 g of Celecoxib Gel 1.5% to each knee, and 2 ± 0.10 g to each hand (total of ~48 g containing 720 mg of celecoxib daily) for 7 days
		Treatment F	4 daily applications of 4 ± 0.10 g of Celecoxib Gel 4% to each knee, and 2 ± 0.10 g to each hand (total of ~48 g containing 1920 mg of celecoxib daily) for 7 days

In both parts, safety was assessed throughout the study; parameters included the frequency of treatment-emergent adverse events (TEAEs) and their severity and relationship to the IMP, clinical laboratory abnormalities, vital signs abnormalities, and electrocardiogram (ECG) abnormalities. In addition, subjects underwent skin irritation assessments (comprised of a dermal response scoring system and other effects scoring system) at 24 hours after the IMP application in Part I, and approximately 24 hours after the first IMP application of day 1 and approximately 12 hours after the last IMP application of day 7 in Part II.

2.3.2.2. Study 2019-4679 Summary of Results

A total of 66 healthy adult subjects received IMP during the study; 18 subjects received a single dose of IMP in Part I, and 48 subjects received multiple doses of IMP over 7 days in Part II.

PK Summary

A summary of celecoxib PK parameters following administration of single (Part I) and multiple doses of celecoxib (Part II) is provided in Table 2. The following overview focuses on the highest

dose of Celecoxib Gel (i.e., 4%) administered under single (Treatment B) and multiple dose conditions (Treatment D and Treatment F).

Following single administration of Celecoxib Gel 4% (Treatment B), the average peak exposure, as measured by mean C_{max}, was 0.747 ng/mL (Coefficient of Variation [CV], 92%). This value is approximately 940 times lower than the peak exposure measured following a single oral dose of celecoxib 200 mg (705 ng/mL) (Davies *et al.* 2000; Celebrex CPM 2022). In Treatment group D (i.e., a dose schedule most closely resembling that in the planned Phase 2 study), mean C_{max} was 1.212 ng/mL (CV 36%) on Day 1, and 2.477 ng/mL (CV 62%) on Day 7. At the highest dose intensity administered in Treatment F (~48 grams of Celecoxib Gel containing 1920 mg of celecoxib applied daily), mean C_{max} was 3.210 ng/mL (CV 62%) on Day 1, and 7.375 ng/mL (CV 59%) on Day 7 (data not shown in Table 2). Published PK data for oral celecoxib 200 mg administered under similar multiple-dose conditions are not available; however, the C_{max} levels detected following administration of Celecoxib Gel 4% on Day 1 in Treatment groups D and F respectively, were approximately 582 and 220 times lower than the peak exposure measured following a single oral dose of celecoxib 200 mg.

Following single administration of Celecoxib Gel 4% (Treatment B), the average systemic exposure of celecoxib, as measured by mean AUC_t and AUC_{inf}, was 48.165 ng·h/mL (CV 70%) and 52.880 ng·h/mL (CV 56%), respectively. In comparison, the reported mean AUC value measured following a single oral dose of celecoxib 200 mg was 7830 ng·h/mL (Davies *et al.* 2000), i.e., approximately 148 to 163 times higher.

Mean T_{max} and $T_{1/2}$ were approximately 42 and 49 hours, respectively, after a single application of Celecoxib Gel 4% (Treatment B) compared to 2.8 and 11.2 hours, respectively, following a single oral dose of celecoxib 200 mg) (Davies *et al.* 2000; Celebrex CPM 2022).

The percent of celecoxib recovered in the urine over 48 hours was negligible after a single application of Celecoxib Gel at either dose strengths.

Table 2 Summary of Celecoxib PK Parameters Following Administration of G001, Study 2019-4679

		Part I		Part II, Cohort 1		Part II, Cohort 2	
		A N = 9	B N = 9	C N = 12	D N = 12	E N = 12	F N = 12
C_{max} (ng/mL)	Arithm. Mean (CV%)	0.276 (90)	0.747 (92)	1.144 (101)	1.817 (70)	4.075 (130)	5.293 (74)
	Geometric Mean	0.198	0.490	0.758	1.552	2.495	4.099
AUC_t (ng·h/mL)	Arithm. Mean (CV%)	15.052 (72)	48.165 (70)	-	-	-	-
	Geometric Mean	12.059	34.852	-	-	-	-
AUC_{inf} (ng·h/mL)	Arithm. Mean (CV%)	14.856 (73)	52.880 (56)	-	-	-	-
	Geometric Mean	12.202	44.597	-	-	-	-
AUC_{24} (ng·h/mL)	Arithm. Mean (CV%)	2.231 (67)	5.935 (76)	15.912 (111)	25.276 (88)	49.897 (110)	79.574 (70)
	Geometric Mean	1.818	3.805	9.497	19.087	32.758	61.183
AUC_{24} Accumulation Ratio (Day 7 vs Day 1)		N/A	N/A	673.57	335.51	315.81	302.12
T_{max} (hr), Mean (CV%)	Day 1	34.67 (39)	41.93 (40)	22.50 (10)	24.01 (<1)	19.01 (26)	18.67 (25)

		Part I		Part II, Cohort 1		Part II, Cohort 2	
		A N = 9	B N = 9	C N = 12	D N = 12	E N = 12	F N = 12
	Day 7	-	-	16.40 (52)	13.45 (61)	8.58 (89)	10.17 (69)
$T_{1/2}$ (hr), Mean (CV%)	Day 1	38.60 (50)	49.23 (40)	-	-	-	-
CL (L/hr), Mean (CV%)		11818.2 (67)	8761.2 (70)	-	-	-	-
Ae_{48} (Part I) or Ae_{24} (Part II) (ng), Day 1	Mean (SD)	649.89 (1438.69)	751.18 (778.69)	444.78 (550.89)	4272.81 (12691.16)	7175.88 (17225.88)	7220.26 (20487.98)
	Geometric Mean	160.09	337.89	244.90	699.91	1002.29	1291.72
Ae_{48} (Part I) or Ae_{24} (Part II) (ng), Day 7	Mean (SD)	N/A	N/A	355.32 (292.58)	919.27 (1440.18)	2658.12 (3894.88)	11953.97 (24260.89)
	Geometric Mean	N/A	N/A	267.65	365.26	1256.65	2509.50

Abbreviations: A_{e24} = urinary excretion over 24 hours; AUC_{inf} = area under the concentration versus time curve for the interval from time zero hour to infinity; AUC_t = area under the concentration versus time curve for the interval from zero hour to the last measurable time point; AUC_{24} = area under the concentration versus time curve for the interval from zero hour to 24 hours; CL=the apparent total body clearance of drug after topical application (CL=Dose/AUC_{inf}); C_{max} = maximum measured plasma analyte concentration; CV=coefficient of variation; SD=standard deviation; T_{max} = time of the maximum measured plasma analyte concentration; $T_{1/2}$ = elimination half-life

Values are rounded to 3 decimal places.

Safety Summary

The administration of the IMP was generally well tolerated. No deaths or serious adverse events (SAEs) occurred during the study. The proportion of subjects who experienced at least one TEAE was 28% in Part I (Treatment A: 22%; Treatment B: 33%), 75% in Part II, Cohort 1 (Treatment C and D: 75% each), and 33% in Part II, Cohort 2 (Treatment E: 25%; Treatment F: 42%); refer to Table 3 for details. All TEAEs reported during the study were mild in severity. With the exception of 1 TEAE of urticaria for which the event outcome was unknown (subject was lost to follow-up), all TEAEs resolved prior to end-of-study (EOS). Four of 66 (6%) subjects (all in Part II, Cohort 1) were taking concomitant medications during the study, for the treatment of AEs (most commonly fever).

Table 3 Summary of Treatment-Emergent Adverse Events Reported in Study 2019-4679

	Reported Incidence by Treatment Group n (%) of Subjects					
	Part I		Part II, Cohort 1		Part II, Cohort 2	
	A N = 9	B N = 9	C N = 12	D N = 12	E N = 12	F N = 12
Any TEAEs	2 (22.2%)	3 (33.3%)	9 (75.0%)	9 (75.0%)	3 (25.0%)	5 (41.7%)
Drug-related AEs	2 (22.2%)	3 (33.3%)	2 (16.7%)	2 (16.7%)	0 (0%)	1 (8.3%)
Application site adverse reactions	0 (0%)	2 (22.2%)	2 (16.7%)	2 (16.7%)	0 (0%)	1 (8.3%)
SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs leading to early discontinuation [a]	0 (0%)	0 (0%)	2 (16.7%)	1 (8.3%)	0 (0%)	0 (0%)
Drug-related AEs leading to discount.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe TEAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Reported Incidence by Treatment Group n (%) of Subjects					
	Part I		Part II, Cohort 1		Part II, Cohort 2	
	A N = 9	B N = 9	C N = 12	D N = 12	E N = 12	F N = 12
TEAEs Occurring at a Frequency of ≥10% in any Treatment Group						
Application site erythema	0 (0%)	1 (11.1%)	2 (16.7%)	2 (16.7%)	0 (0%)	1 (8.3%)
Application site rash	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	1 (11.1%)	1 (11.1%)	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)
Heart rate increased	0 (0%)	0 (0%)	4 (33.3%)	3 (25.0%)	0 (0%)	0 (0%)
Influenza like illness	0 (0%)	0 (0%)	2 (16.7%)	0 (0%)	0 (0%)	0 (0%)
Nasal congestion	0 (0%)	1 (11.1%)	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)
Neutrophil count decreased	1 (11.1%)	0 (0%)	0 (0%)	2 (16.7%)	0 (0%)	0 (0%)
Pyrexia	1 (11.1%)	0 (0%)	3 (25.0%)	1 (8.3%)	0 (0%)	0 (0%)
White blood cell count decreased	1 (11.1%)	0 (0%)	0 (0%)	2 (16.7%)	0 (0%)	0 (0%)

Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Part I

All 18 subjects randomized in Part I completed the study as per protocol. An overall summary of TEAEs is provided in Table 3.

Drug-related AEs: Five subjects (28%) experienced 7 TEAEs that were deemed possibly related to the IMP. Two subjects (22%) in Treatment A experienced drug-related TEAEs of headache, pruritus, neutrophil count decreased, and white blood cell decreased, and 3 subjects (33%) in Treatment B experienced 3 drug-related TEAEs of application site erythema, application site rash, and headache. One subject who had neutrophil count decreased and white blood cell decreased after Treatment A presented with low leukocytes and neutrophils at Baseline.

Other Safety Assessments: There were no consistent and clinically meaningful changes in mean laboratory values over time. Increases of >10% in mean serum bilirubin levels were detected in both Treatments A and B; however, all mean bilirubin levels remained within normal range. There were no consistent and clinically meaningful changes in mean vital signs or ECG parameters, including no indication of QT or QTcB prolongation, and no individual clinically significant (CS) vital signs or ECG abnormalities were reported as AEs. All physical examinations results were reported as normal in Part I.

Skin Irritation: Skin irritation was evaluated approximately 24 hours after the IMP application and showed a Dermal Response Score of 0 (no evidence or irritation) and no "Other" effects, yielding mean ± SD Cumulative Irritation Scores of 0 ± 0 in both treatment groups.

Part II, Cohort 1

Ten of 12 subjects (83.3%) randomized to Treatment C, and 11 of 12 subjects (91.7%) randomized to Treatment D completed treatment as per protocol. Three subjects (12.5%) discontinued due to TEAEs, including two subjects who received Treatment C (pyrexia and influenza like illness in one subject and pyrexia in the second subject), and one subject who received Treatment D (pyrexia and feeling hot). All five events were assessed by the Investigator as unrelated to the IMP.

An overall summary of TEAEs is provided in Table 3.

Drug-related AEs: Eleven TEAEs occurred in 4 subjects (16.7%) and were assessed as drug-related. All events were application site adverse reactions; 2 subjects in Treatment C experienced 7 drug-related TEAEs (three events each of application site erythema and application site pain, and one event of application site hypersensitivity), and 2 subjects in Treatment D experienced 4 drug-related TEAEs (two events of application site erythema, and one event each of application site hypersensitivity and application site irritation).

Other Safety Assessments:

Changes >10% in mean serum bilirubin (increase), leukocytes, and neutrophils (reduction) were detected with in both treatments treatment groups throughout the study; changes were also detected in mean transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and triglycerides levels at some of the assessments timepoints for Treatment D. However, the clinical relevance of these changes is considered minimal, and none are indicative of a safety concern related to the IMP. Five subjects (21% of subjects dosed in Part II, Cohort 1) exhibited a total of 14 CS laboratory values that were reported as AEs. The frequency of these events was similar in the two groups (C and D). The most common CS laboratory abnormalities were white blood cell count decreased and neutrophil count decreased (2 subjects [8.3% of subjects in Part II, Cohort 1], 3 events each) following Treatment D. All laboratory AEs in Part II, Cohort 1 were assessed by the Investigator as mild and unrelated or unlikely related to the IMP.

Increases in mean (and median) pulse rate were observed, including increases >20% at some assessment timepoints with both treatments (C and D). There were no other consistent or clinically meaningful changes in mean vital signs measurements. Clinically significant vital signs abnormalities (reported as AEs) occurred in 10 subjects (41.7%) treated in Part II, Cohort 1, and included heart rate increased (4 [33.3%] subjects in Treatment C and 3 [25.0%] subjects in Treatment D), pyrexia (3 subjects [25.0%] and 1 subject [8.3%], respectively), and blood pressure increased (0 and 1 subject [8.3%], respectively). All CS vital sign abnormalities were assessed by the Investigator as mild and unrelated to the IMP.

There were no consistent or clinically meaningful changes over time in any of the ECG parameters, including no indication of QT or QTcB prolongation with either Treatment C or D. One CS ECG abnormality was detected in each group: electrocardiogram PR prolongation in one subject in Treatment C, and heart rate decreased in one subject in Treatment D. Both events started >6 days after IMP application, resolved within 7 days without intervention, and were assessed by the Investigator as mild and unrelated to the IMP. Clinically significant physical examination abnormalities (reported as AEs) occurred in two subjects in Treatment C (application site dryness and nasal congestion).

Skin Irritation: Mean ± SD Cumulative Irritation Scores were 0.0 ± 0.0 in both groups (Treatment C and Treatment D) on Day 2 (approximately 24 hours after the first IMP application), and 0.1 ± 0.32 in the Treatment C group and 0.0 ± 0.0 in the Treatment D group on Day 8 (approximately 12 hours after the last IMP application). One subject (8.3%) in Treatment C had a Dermal Response Score of 1 (minimal erythema, barely perceptible), with an A(0) designation (defined as slightly glazed appearance) for "Other" Effects on Day 8.

Part II, Cohort 2

All 24 subjects randomized in Part II, Cohort 2 completed the study as per protocol. An overall summary of TEAEs is provided in Table 3.

Drug-related AEs: One subject (4.2%; Treatment F) experienced two TEAEs that were assessed as possibly related to the IMP; both were application site adverse reactions (application site erythema and application site dryness).

Other Safety Assessments:

At some of the assessments timepoints, increases >10% in mean serum bilirubin values were detected with both treatments (E and F) and reductions in mean neutrophil and leukocyte values were detected with Treatment F. However, apart from a borderline elevation in one subject, all bilirubin levels remained within normal range. Overall, these changes are of minimal clinical relevance and are not indicative of a safety concern related to the IMP.

There were no consistent or clinically meaningful changes over time in any of the ECG parameters, including no indication of QT or QTcB prolongation with either treatment (E or F). Clinically significant ECG abnormality occurred in 1 subject (8.3%) in Treatment E (supraventricular extrasystoles 27 days after the last IMP application; assessed as mild and unrelated to the IMP). No clinically significant ECG abnormality occurred with Treatment F. All physical examination results were reported as normal in Part II, Cohort 2.

Skin Irritation: Mean ± SD Cumulative Irritation Scores were 0.0 ± 0.0 in both groups (Treatment E and Treatment F) on Day 2 (approximately 24 hours after the first IMP application), and 0.0 ± 0.0 in the Treatment E group, and 0.08 ± 0.29 in the Treatment F group on Day 8 (approximately 12 hours after the last IMP application). One subject (8.3%) in Treatment F had a Dermal Response Score of 1 (minimal erythema, barely perceptible), with no "Other" effects on Day 8.

The following is a complete list of application site reactions reported in Study 2019-4679: application site erythema, application site hypersensitivity, application site pain, application site irritation, application site dryness, application site rash, or application site bruise.

2.3.2.3. Blinded Interim Safety Update from Study 2020-G001

A total of 200 (of the planned 210) patients with primary symptomatic OA of the knee have been randomized (1:1) to G001 or vehicle gel up to the data cut-off date of 31 August 2022. Given that recruitment and blinded treatment and assessments are still ongoing, the current safety update for this study is limited to a *blinded* summary of TEAE data (G001 and vehicle groups combined) as of the data cut-off date.

Based on *blinded* safety data collected to date, the study drug (administered four times per day over four weeks) is well tolerated. Four patients discontinued due to an AE, including hypertension (assessed as mild, and possibly related to *blinded* study treatment), ligament sprain (moderate, unrelated), muscle spasms (moderate, possibly related), and vision blurred (moderate, possibly related). No deaths and no study drug-related SAEs have occurred during the study to date. One SAE (atrial fibrillation) has been reported in a 77-year-old male with a history of hypertension and prior palpitations (self-reported); the event was assessed as mild, and not related to the *blinded* study treatment. Other cardiac events were limited to one non-serious event of extrasystoles in a 66-year-old female, assessed as moderate and not related to the *blinded* study drug. Two events of (worsening) hypertension (both assessed as mild, and probably related to *blinded* study treatment) required dosing interruption or discontinuation.

In the total population of 200 randomized OA patients at the time of the data cut-off, the overall frequency of TEAEs was 29.0%, with headache being the most common TEAE (6.5% of patients). Overall, the frequency of TEAEs assessed as at least possibly related to the *blinded* study treatment

has been low (9 patients, 4.5%). Of these, only headache and hypertension were reported for more than one patient (2 patients, 1.0%); the remaining related TEAEs occurred in one patient (0.5%) each, and included muscle spasms, administration site dryness, dermatitis contact, folliculitis, and vision blurred. A single application site reaction (application site dryness, assessed as mild, and certainly related to *blinded* study treatment) occurred in the study to date.

For further details, refer to the Investigator's Brochure (G001 IB, 2022).

2.4. Study Rationale

Non-steroidal anti-inflammatory drugs, including oral celecoxib are well established treatments for patients with OA. The similar efficacy of topical NSAIDs to that of oral NSAIDs in the management of OA pain, coupled with a much better safety profile due to the low systemic absorption (Rannou *et al.* 2016) make these treatment modalities a preferred first treatment option for patients with OA (Kolasinski *et al.* 2020). G001 is a novel gel formulation of celecoxib for topical administration, being developed for the treatment of the signs and symptoms of knee and hand OA.

In a Phase 1 double-blind, randomized, parallel-group study (Study 2019-4679), G001 (dose strengths of 1.5% and 4%) was generally well tolerated when administered under single-dose (N=18) or multiple dose conditions (N=48) in adult healthy volunteers. All AEs reported in this study were mild in intensity, and the majority (75%) of the IMP-related AEs were mild and transient application-site adverse reactions. The systemic bioavailability of celecoxib was low after either single- or multiple-dose applications of G001, as compared to oral administrations of celecoxib at the recommended dose for OA treatment (200 mg/day); refer to Section 2.3.2.2 for details.

The current Phase 2 study will provide the first evaluation of the efficacy, safety, and local tolerability of G001 in patients with OA. The study will enroll male or female patients aged 40 years or above with a 6-month documented history of OA of the knee, meeting ACR criteria (see Appendix 1), and radiologic evidence of grade 2 (mild) or grade 3 (moderate) disease according to Kellgren and Lawrence Radiographic Grading (see Appendix 2). The dose strength to be evaluated in this study (4%) was previously assessed in healthy volunteers in Study 2019-4679, and the dosing regimen will closely resemble that in Treatment D in Study 2019-4679, with a longer treatment duration (4 weeks vs 1 week). A rationale for the dose selection is provided in Section 4.4.

Based on the results of this study, the Sponsor plans to further evaluate G001 in Phase 3 clinical trials in patients with OA of the knee and hand.

2.5. Benefit/Risk Assessment

A summary of clinical experience, including AEs reported during administration of G001 in healthy adult subjects enrolled in the Phase 1 Study 2019-4679 is provided in Section 2.3.2.2. Consistent with clinical experience with other topical NSAIDs (Bannuru *et al.* 2019), the reasonably expected AEs of G001 are local, application site reactions. Based on experience from Study 2019-4679, these events may include application site erythema, application site hypersensitivity, application site pain, application site irritation, application site dryness, application site rash, or application site bruise.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of G001 may be found in the Investigator's Brochure (IB) (G001 IB, 2022).

2.5.1. Risk Assessment

An overview of the known risks associated with oral celecoxib, along with an assessment of how these risks may be translated to administrations of G001, and a summary of strategies employed in the current Phase 2 study to mitigate these risks is provided in Table 4.

Further details about the known risks associated with oral celecoxib can be found in the approved Celebrex label (Celebrex CPM 2022), and about the expected risks and reasonably expected AEs of G001 in the IB (G001 IB, 2022).

Table 4 Risk Assessment: Oral vs Topical Celecoxib, Including Risk Mitigation Strategies

Known Risks Associated with Oral Celecoxib (Celebrex CPM 2022)	**Clinical Experience with G001 (Phase 1 Study 2019-4679)**	**Risk Mitigation Strategy in the Current Clinical Study**
Risk of serious (potentially fatal) CV thrombotic events (such as myocardial infarction and stroke/ cerebrovascular bleeding), higher with longer duration of treatment, and in patients with ischemic heart disease, cerebrovascular disease, CHF (NYHA II-IV)	There were no SAEs or thrombotic events, and no findings indicative of increased risk of thrombosis in Study 2019-4679.	[1] Patients with any condition that is listed as contraindication or warning/precaution in the approved prescribing information for celecoxib are excluded from the study; see Section 5.2. Patients with uncontrolled, severe cardiac disease are excluded from the study; see Section 5.2. Treatment duration is limited to 4 weeks. Monitoring of coagulation indices during the study; see SoA and Appendix 5.
Dose-dependent increase in sodium retention (via renal mechanism), resulting in fluid retention, increased BP (new HTN or worsening of pre-existing HTN) and/or exacerbation of CHF.	No notable changes in individual or mean sodium levels over time were detected in Study 2019-4679. There were no notable changes in mean BP measurements over time. One subject (Treatment D) experienced increased BP, assessed as mild and unrelated to the IMP.	As listed under [1] above. Patients with uncontrolled, severe cardiac disease are excluded from the study; see Section 5.2. Monitoring of BP and electrolyte levels during the study; see SoA and Appendix 5.
Risk of hypersensitivity reactions to celecoxib or to any of the components/excipients, including	No systemic hypersensitivity reactions occurred in Study 2019-4679.	As listed under [1] above. Patients with known sensitivity to celecoxib, or any other NSAID, or menthol are

Known Risks Associated with Oral Celecoxib (Celebrex CPM 2022)	**Clinical Experience with G001 (Phase 1 Study 2019-4679)**	**Risk Mitigation Strategy in the Current Clinical Study**
potentially fatal anaphylactoid reactions and angioedema.		excluded from the study; see Section 5.2.
Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction, and gastrointestinal bleeding. The risk is increased 10-fold in patients with a prior history of peptic /duodenal ulcer disease and/or GI bleeding.	No cases of GI ulceration, inflammation, perforation, obstruction, or bleeding, and no other severe GI events occurred in Study 2019-4679.	As listed under [1] above. Patients with documented gastroduodenal ulcer or GI bleeding within the last 6 months or presence of other GI disorder that could put the patient at increased risk, and alcohol abuse within the past year are excluded from the study; see Section 5.2. Treatment duration is limited to 4 weeks. (GI bleeding:) Monitoring of coagulation indices during the study; see SoA and Appendix 5.
Persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis	One subject (Treatment C) experienced urine analysis abnormal (including bacteria and leukocytes in urine), assessed as mild and unrelated to the IMP.	As listed under [1] above. Safety laboratory testing includes urinalysis during the study; see SoA and Appendix 5.
Anemia and other blood dyscrasias (neutropenia, leukopenia, thrombocytopenia, agranulocytosis)	One subject each receiving Treatment C, E and F experienced haematocrit decreased and haemoglobin decreased, and 1 subject receiving Treatment F experienced red blood cell count decreased; all assessed as mild, and unrelated to the IMP. Mild reductions >10% in mean leukocytes, and neutrophils were detected with Treatments C, D, and F. AEs of white blood cell count decreased and neutrophil count decreased occurred in one subject receiving Treatment A (also present pre-treatment; assessed as mild and possibly related to the IMP), and 2 subjects receiving Treatment D (assessed as mild, and unlikely related to the IMP).	As listed under [1] above. Patients with hemoglobin levels <10 g/dL are excluded from the study; see Section 5.2. Hematology testing during the study; see SoA and Appendix 5.

Known Risks Associated with Oral Celecoxib (Celebrex CPM 2022)	**Clinical Experience with G001 (Phase 1 Study 2019-4679)**	**Risk Mitigation Strategy in the Current Clinical Study**
Severe hepatic reactions, including liver necrosis and hepatic failure (with fatal outcomes or requiring liver transplant), fulminant hepatitis (with fatal outcome), cholestatic hepatitis (with fatal outcome) and jaundice [rare cases] Abnormal liver function tests: borderline elevations of one or more liver enzyme tests (AST, ALT, ALP) may occur in up to 15% of patients	Mild increases >10% in mean transaminases (ALT and AST) were observed with Treatment D at some of the assessments timepoints. Elevated ALT (up to 140 IU/L) and AST (up to 341 IU/L) occurred in 1 subject receiving Treatment C; the events were assessed as mild, and unrelated to the IMP.	As listed under [1] above. Patients with severe hepatic disease, and patients with screening AST, ALT, or GGT levels ≥ 2 times the ULN are excluded from the study; see Section 5.2. Safety laboratory testing includes liver function tests during the study; see SoA and Appendix 5. As a standard precautionary measure, this protocol includes liver chemistry stopping criteria and reporting requirements; see Section 7.1.1.
Severe renal impairment: acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome and acute glomerulonephritis; renal insufficiency in patients with pre-renal conditions (Fluid and electrolyte balance: see above)	There were no AEs or laboratory findings indicative of renal impairment in Study 2019-4679.	As listed under [1] above. Patients with severe renal disease and patients with screening serum creatinine ≥ 1.5 times the are excluded from the study; see Section 5.2.
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [rare cases]	No severe skin reactions occurred in Study 2019-4679.	As listed under [1] above. Study assessments include skin irritation tests during the study; see SoA and Appendix 4.
Respiratory: pneumonitis (some serious), ASA-induced asthma	No respiratory AEs occurred in Study 2019-4679.	As listed under [1] above. Patients with severe systemic disease are excluded from the study; see Section 5.2.
Impaired fertility	Not evaluated in Study 2019-4679.	As listed under [1] above. Patients who are currently pregnant or planning to be become pregnant are excluded from the study; see Section 5.2.
Risk in pregnancy / fetal exposure: Risk of premature closure of the ductus arteriosus and uterine inertia/prolonged	Not evaluated in Study 2019-4679. Pregnant subjects were	As listed under [1] above. Patients who are currently pregnant or planning to be

Known Risks Associated with Oral Celecoxib (Celebrex CPM 2022)	Clinical Experience with G001 (Phase 1 Study 2019-4679)	Risk Mitigation Strategy in the Current Clinical Study
parturition. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure.	excluded, and no pregnancy occurred during the study.	become pregnant are excluded from the study; see Section 5.2.
Potential for serious adverse reactions in nursing infants	Not evaluated in Study 2019-4679. Breastfeeding subjects were excluded from the study.	As listed under [1] above. Patients who are breast-feeding are excluded from the study; see Section 5.2.

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASA=acetylsalicylic acid; AST=aspartate aminotransferase; BP=blood pressure; CHF=congestive heart failure; CV=cardiovascular; GGT=gamma-glutamyl transferase; GI=gastrointestinal; HTN=hypertension; NSAID=nonsteroidal anti-inflammatory drug; NYHA=New York Heart Association; SAE=serious adverse event; ULN=upper limit of normal

2.5.2. Benefit Assessment

The potential benefits of participating in the current study for individual participants may include the following:

- Potential benefit of receiving study treatment during the 4-week study duration that may have clinical utility
- Contributing to the process of developing new therapies in an area of unmet need
- Medical evaluations/assessments associated with study procedures (e.g., physical exam, ECG, safety laboratory evaluations, etc.)

2.5.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with G001 are justified by the anticipated benefits that may be afforded to patients with OA of the knee.

3. Objectives and Endpoints

The objective of this study is to evaluate the efficacy, safety, and local tolerability of G001 compared to vehicle in patients with symptomatic OA of the knee.

Specific objectives and corresponding endpoints for the study are outlined in Table 5.

Table 5 Study Objectives and Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy	
• To evaluate the efficacy of G001 compared to vehicle in patients with symptomatic OA of the knee, as measured by the WOMAC Pain Subscale Score	• Change from Baseline in WOMAC Pain Subscale Score at Week 4/EOT
Secondary Efficacy	
• To further evaluate the efficacy of G001 compared to vehicle in patients with symptomatic OA of the knee, as measured by the WOMAC Physical Function Subscale, Stiffness Subscale, and Total scores; 11-point pain NRS scores, PGA and IGA of disease activity and overall treatment benefit, and rescue medication use	• Mean worst *daytime* and mean worst *nighttime* pain severity scores (11-point pain NRS, from patient diary) at Week 4/EOT and Week 5/FV2, including mean changes from Baseline • Percentages of patients achieving ≥20%, ≥30%, and ≥50% reduction from Baseline in worst *daytime* pain severity scores (11-point pain NRS, from patient diary) at Week 4/EOT • Percentages of patients achieving ≥20%, ≥30%, and ≥50% reduction from Baseline in worst *nighttime* pain severity scores (11-point pain NRS, from patient diary) at Week 4/EOT • Change from Baseline to Week 4/EOT in WOMAC Physical Function Subscale score • Change from Baseline to Week 4/EOT in WOMAC Total score • Change from Baseline to Week 4/EOT in WOMAC Stiffness Subscale score • Change from Baseline to Week 2 in WOMAC Total and Subscale scores • Change from Week 4/EOT to Week 5/FV2 in WOMAC Total and Subscale scores • Change from Baseline in PGA of disease activity over time • Change from Baseline in IGA of disease activity over time • PGA and IGA of overall treatment benefit at Week 2 and Week 4/EOT • Incidence of rescue medication use, number of doses, and percentage of days with any rescue medication use during the last week of study treatment, and overall during the study treatment period (between the first and last study drug dose dates).

Safety	
• To evaluate the overall safety of G001 in patients with symptomatic OA of the knee, as determined by AE reporting, vital signs and ECG measurements, and physical examinations	• Frequency and severity of AEs, study drug-related AEs, SAEs, and AEs leading to study drug discontinuation • Changes in safety laboratory test results, vital signs measurements, 12-lead ECG, and physical examination findings
• To evaluate the local tolerability of G001 in patients with symptomatic OA of the knee, as determined by AE reporting, and skin irritation test scores	• Frequency and severity of application site AEs • Skin irritation test scores at Week 2, Week 4/EOT, and Week 6/EOS

4. Study Design

4.1. Overall Design

Study 2020-G001-P2 is a Phase 2 multicenter, double-blind, randomized, parallel-group, vehicle-controlled study to evaluate the efficacy, safety, and local tolerability of G001 compared to vehicle in patients with symptomatic OA of the knee.

A total of 210 patients with primary OA of the knee and moderate OA pain are planned to be enrolled at approximately 10 centres located in Canada (Quebec and Ontario). Each patient's participation will be approximately 7 weeks (~1 week screening, 4 weeks of treatment, and 2 weeks of post-treatment follow-up). Additional pre-screening time (after informed consent was obtained) may be required for washout periods and radiological examination. The overall study duration (from first patient first visit [FPFV] to last patient last visit [LPLV]) is expected to be about 6 months.

Following screening, prior NSAID and/or acetaminophen use will be discontinued to allow for washout (3 to 7 days) and symptom flare. Acetaminophen may be used as rescue medication only, except within 12 hours prior to the Baseline/Flare Visit #1 (FV1). Patients will be instructed to rate their worst daytime and nighttime pain in their Screening Diary, as well as to document any rescue medication (acetaminophen) used for breakthrough pain.

Eligible patients with adequate OA pain in the index knee at the Baseline/FV1 visit will be randomly assigned to one of two treatment groups (Group 1: G001 4.0%; Group 2: Vehicle) in a 1:1 allocation ratio.

Patients will be instructed to apply 4 grams of the IMP (test or reference product) to the index knee (i.e., knee selected for study treatment) four times daily for four weeks. Patients will also be instructed to rate their worst daytime and nighttime pain in their Treatment Diary, as well as to document the date and time of each IMP application, and any rescue medication (acetaminophen) use. No rescue medication use is allowed within 12 hours prior to an efficacy assessment.

Patients will return to the clinic twice during the treatment period for efficacy and safety assessments: at Week 2 (after 14 ± 1 day of study treatment), and at Week 4/End-of-Treatment (EOT; after 28 ± 2 days of study treatment). During these visits, patients will undergo the following efficacy assessments: WOMAC Index, Patient Global Assessment (PGA), Investigator Global Assessment (IGA), and review of patient diary. In addition, the Investigator (or qualified designee) will contact the patient by phone after one week of treatment (Week 1, study Day 8 ± 1), and after three weeks of treatment (Week 3, study Day 22 ± 1), to verify compliance with the study drug application and daily diary completion requirements, and to follow up on how the IMP is tolerated.

Safety assessments will include recording of AEs and concomitant medications, safety laboratory tests (complete blood count [CBC], blood chemistry, coagulation tests, and urinalysis), 12-lead ECG, physical examination and vital signs measurements, and skin irritation testing.

Patients will return to the clinic 3 to 7 days after the last IMP application for a second Flare Visit (Week 5/FV2), and within approximately 2 weeks after the last IMP application (Week 6; study Day 43 ± 3) for an EOS evaluation. Daily diary completion will continue (as described above) until the Week 5/FV2 visit.

Patients who discontinue study treatment prematurely will be asked to return to the clinic for EOT assessments at the time of withdrawal, and the EOS evaluations 14 ± 2 days after the last study drug application, unless the patient withdraws consent from any further study participation.

4.2. Scientific Rationale for Study Design

The design of this study was developed in accordance with the current Osteoarthritis Research Society International (OARSI) recommendations for design, conduct, and reporting of clinical trials for knee OA (McAlindon *et al*. 2015), and taking into consideration the current ACR guidelines for the management of OA (Kolasinski *et al.* 2020).

Parallel-group, randomized, placebo-controlled trials are considered gold standard study designs, including in OA research (McAlindon *et al*. 2015). The current study will evaluate the efficacy, safety, and tolerability of G001 compared to the vehicle formulation. To mitigate selection bias, eligible patients will be randomized using an interactive web response system (IWRS) to one of two treatment groups in a 1:1 allocation ratio. A separate blinding protocol will be in place to ensure that patients and clinic staff involved in assessing the study outcomes remain unaware of the treatment allocation.

A major goal of early phase efficacy studies is to enroll a well-defined, homogenous population, most likely to benefit from the study treatment (McAlindon *et al*. 2015). Therefore, the study will enroll adult patients at least 40 years of age, with an established diagnosis of OA of the knee according to standard diagnostic (ACR) criteria and a disease duration of at least 6 months. In addition, as recommended for studies of symptom-modifying drugs, the study population will have sufficiently advanced OA, with radiologic evidence of mild or moderate disease (grade 2 or 3) according to internationally recognized and utilized Kellgren and Lawrence Radiographic Grading (Kellgren and Lawrence, 1957; Petersson *et al.* 1997). The exclusion criteria have been defined to minimize interference of comorbidities with the pain and functional assessments planned in this study, as well as to mitigate the known risks associated with oral formulations of celecoxib.

As recommended for studies of symptomatic response (McAlindon *et al*. 2015), the screening pain threshold has been selected to allow for detection of change between Screening and Baseline/FV1, as well as to optimize the chances of detecting a minimally clinically important difference (MCID) in the primary endpoint measure during the treatment period. The index joint (target joint for study treatment) will be selected based on symptom severity. To minimize the risk of pain inflation during the Screening period, research staff will be trained not to disclose information about the minimal pain thresholds to prospective study patients under any circumstances.

Given that patient-reported outcome responses may differ between patients with unilateral and bilateral knee OA (Riddle and Stratford, 2013; Kahn *et al*. 2014; Cotofana et al. 2015), and that WOMAC scores are most strongly associated with pain intensity in patients with unilateral (compared to bilateral) pain (Riddle and Stratford, 2013), the pain threshold in the contralateral knee will be limited to ≤2 on the 11-point pain Numerical Rating Scale (NRS) to minimize interference with the assessments in the index knee.

Symptomatic outcomes will be assessed based on WOMAC (5-point Likert format), 11-point pain NRS, and global assessment measures (PGA, IGA) of disease activity and treatment benefit, with the WOMAC Pain Subscale selected as primary endpoint measure. The WOMAC is a validated, and widely utilized patient-reported outcome measure of pain, stiffness, and function in patients

with OA of the knee or hip (Bellamy *et al*. 1988; Bellamy 1997; Bellamy 2002); see Section 4.3. Given that concomitant or rescue pain medication may improve patient-reported outcome assessments independent of a treatment effect, several measures will be included to control for these adverse influences: (1) washout periods for prior oral, intramuscular, or intra-articular corticosteroids; (2) discontinuation of NSAID and acetaminophen treatment at Screening (to prompt a flare during the Screening period); (3) prohibition of other analgesic use during the study; (4) standardized use of rescue medication (acetaminophen), including maximum individual dose and daily limits; (5) restrictions in concomitant analgesic use will continue through Week 5/FV2 (3 to 7 days after the last IMP application), to detect changes in pain scores and in rescue medication use during the week after study drug discontinuation. The purpose of the Week 5/FV2 visit is to capture any worsening in symptomatic outcomes after discontinuation of study treatment.

4.3. Justification for the Primary Efficacy Measure

The primary efficacy endpoint is the change from Baseline in WOMAC Pain Subscale Score at Week 4/EOT. The WOMAC® 3.1 Index in 5-point Likert format will be used in this study; see Appendix 3.

The WOMAC is one of the most widely utilized self-report measures of lower extremity symptoms and function (Bellamy *et al*. 1988; Bellamy 1997; Bellamy 2002). Its purpose is to assess pain, stiffness, and physical function in patients with hip and/or knee OA. The WOMAC has been used for almost 30 years in many different contexts and patient populations, and there are abundant data regarding its utility and measurement properties.

The WOMAC consists of 24 items divided into 3 subscales: Pain (5 items), Stiffness (2 items), and Physical Function (17 items). Scoring instructions are provided in the WOMAC® 3.1 User Guide XI. The WOMAC Pain Subscale score is derived by summing the five pain scores on the WOMAC OA Index (pain during walking, using stairs, in bed, sitting or lying, and standing), each measured on a 5-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe, and 4=extreme). The maximum WOMAC Pain Subscale rating is 20 and higher scores indicate worse pain; refer to Section 8.2.1 and Appendix 3 for details.

The WOMAC Total score is the sum of the items for all three subscales, with higher scores indicative of worse pain, stiffness, and functional limitations. The maximum WOMAC Total score is 96.

It has been well documented that the WOMAC is a valid and reliable measure, responsive to change in patients with knee OA (Bellamy *et al*. 1988; Davies *et al*. 1999; Roos et al 1999; Bischoff-Ferrari *et al*. 2005; Salaffi et al. 2005).

4.3.1.1. Clinically Important Differences

In a study of patients with hip and knee OA undergoing comprehensive inpatient rehabilitation, the MCIDs for WOMAC global and subscale scores ranged from 0.51-1.33 (1.10 for the Pain Subscale) for worsening and 0.67-0.75 for improvement (0.75 for the Pain Subscale), on a 0-10 scale (Angst *et al*. 2001). In a study of outpatients with knee or hip OA, the MCIDs on pain VAS (0-100 mm) ranged from -7.9 mm to -32.6 mm (Tubach *et al*. 2005). Based on these two studies, investigators used three definitions of MCID to calculate the frequency of clinically important improvement in function over 30 months in Multicenter Osteoarthritis Study (MOST) participants

(White *et al*. 2010). The three definitions were: MCID 26% (26% improvement from Baseline), MCID 17% (17% improvement from Baseline), and MCID tertiles (low, medium, and high, based on pre-specified criteria). In that study, 24-39% of participants reached MCID based on these criteria (White *et al*. 2010), suggesting that a clinically important improvement is frequent in individuals with or at high risk for knee OA. MCID values must be viewed cautiously because of limitations in methodology for calculating these values and should not be considered absolute thresholds.

On the basis of the Osteoarthritis Research Society International–Outcome Measures in Rheumatology (OMERACT-OARSI) responder criteria, the authors of a recent systematic review and network meta-analysis (Bannuru *et al.* 2015) of pharmacologic interventions in knee OA prespecified an absolute change of 20 points on a scale of 0 to 100 as clinically significant improvement (Pham *et al.* 2004).

4.4. Justification for Dose

The current Phase 2 study will evaluate the efficacy, safety, and local tolerability of G001 (Celecoxib Gel 4% for topical administration) in adult patients with symptomatic OA of the knee. As detailed in Section 2.3.2, first-in-human evaluation of the safety, tolerability, and PK of two dose strengths of Celecoxib Gel (1.5% and 4%) applied under single- and multiple dose conditions were completed in adult healthy volunteers as part of the double-blind, randomized, parallel-group, single- and multiple-dose Study 2019-4679. The results of this study indicate that systemic exposure to celecoxib is very low following application of multiple daily doses of Celecoxib Gel even under maximum dose conditions (4% dose strength administered to both knees and both hands four times daily for seven days), and that both dose strengths are well tolerated under single- and multiple-dose application.

The 4% concentration represents the high end of the concentration range for the product. The range was selected empirically taking into consideration the oral dose and the concentrations in topical formulations of other NSAIDs widely used in the treatment of acute musculoskeletal pain, as well as the physical properties of the drug product.

Evidence from RCTs as well as systematic reviews and meta-analyses support the comparable efficacy of the recommended oral doses of celecoxib (200 mg daily) and diclofenac (150 mg daily) in patients with OA (McKenna *et al.* 2001; Bannuru *et al*. 2015; Puljak *et al.* 2017), as well as between oral and topical NSAIDs (Tugwell *et al*. 2004; Simon *et al.* 2009; Puljak *et al.* 2017). The celecoxib doses administered to the index knee with the application of the 4% formulation of Celecoxib Gel (G001) is 160 mg per individual dose, and 840 mg per day. In comparison, the individual and daily doses of diclofenac applied through the administration of marketed topical diclofenac products are approximately 32 mg and 128 mg, respectively, for diclofenac sodium topical solution (Pennsaid Topical Solution 1.5%), and 40 mg and 160 mg, respectively for diclofenac sodium gel (Voltaren Gel 1%). Overall, this data indicate that, compared to the approved diclofenac formulations, the celecoxib doses expected to be delivered ***locally*** (on a mg basis) will be about 3 to 6.6 times higher with G001.

The considerably lower systemic exposure to celecoxib (based on C_{max} and AUC_{24}) following multiple (7-day) applications of G001 compared to the systemic exposure to diclofenac following an identical 7-day dosing regimen of diclofenac sodium gel 1% (Kienzler *et al.* 2010) indicate

that higher doses of G001 can be applied locally (for a potentially better local effect) without the enhanced risks of higher systemic exposure.

4.5. Justification for the Reference Product / Control Group

The reference product in this study will be the Vehicle formulation, containing all excipients of the G001 (including L-menthol 1.5%), but without celecoxib. L-menthol is added to the formulation as a solubilizer and permeation enhancer. Menthol is a widely used penetration enhancer in topical and transdermal formulations due to its high efficiency and relative safety (Joshi et al. 2017; Nagai et al. 2019). Menthol is also well known for its ability to elicit cold sensations. The subjective cooling effect has been reported to last up to ~80 minutes in some subjects (mean around an hour) (Yosipovitch *et al.* 1996; Lasanen *et al*. 2016).

Due to the characteristic cooling effect and odor of menthol in the test formulation, a vehicle formulation with the same amount of menthol (as opposed to a placebo with no menthol) was selected as control treatment to maintain the blind of the treatment allocations.

4.6. End of Study Definition

The end of the study is defined as the date of the last scheduled study assessment (as shown in the SoA; Section 1.3) for the last patient in the trial.

A patient is considered to have completed the study if he/she has completed all phases of the study, including the last study visit (Week 6/EOS visit) as shown in the SoA (Section 1.3).

5. Study Population

A total of 210 patients with primary OA of the knee and moderate OA pain are planned to be enrolled in the study.

Prospective study patients must meet all inclusion criteria (see Section 5.1) and none of the exclusion criteria (see Section 5.2) to qualify for enrolment. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be permitted.

5.1. Inclusion Criteria

Patients must meet all of the following criteria to qualify for the study:

1. Male or female age ≥40 years
2. Documented diagnosis of OA of the knee, meeting ACR criteria for classification of idiopathic (primary) OA (see Appendix 1) for at least 6 months prior to Screening
3. Radiologic evidence of OA of the knee of grade 2 (mild) or grade 3 (moderate) according to Kellgren and Lawrence Radiographic Grading (see Appendix 2)
4. Worst daily pain (within 24 hours prior to Screening and Baseline) in the index knee between 4 and 8 on the 11-point pain NRS
5. On stable analgesic therapy (i.e. at least 3 days per week for at least 30 days prior to Screening) with an oral or topical NSAID and/or acetaminophen
6. In reasonably good general health (apart from OA), as assessed by the Investigator
7. Females of childbearing potential: adequate birth control and negative pregnancy test at Screening and Baseline.

   A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 24 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the Investigator (e.g., Müllerian agenesis).

   Adequate birth control is defined as: stable dose of an oral contraceptive for at least 2 months prior to the first study drug administration, intrauterine device, bilateral tubal ligation, barrier method of contraception in conjunction with spermicidal jelly, or abstinence.
8. Negative urine drug screen (including for cannabinoids) at Screening and Baseline
9. Subject is willing to participate in the study, comply with the study requirements and voluntarily provide written informed consent.

Additional Inclusion Criteria Assessed at Baseline/Flare Visit #1 (FV1):

Following Screening, prior NSAID and acetaminophen use will be discontinued to allow for washout (3 to 7 days) and symptom flare. Acetaminophen may be used as rescue medication only, with the following exception: no rescue medication is allowed within 12 hours prior to the Baseline/FV1 visit.

10. Development of a flare of pain following washout of stable analgesic (NSAID and/or acetaminophen) therapy, defined as follows:
    a. An increase of ≥2 points (out of possible 20) from the Screening assessment in the WOMAC Pain Subscale score for the index knee; and
    b. A score of ≥2 points (out of possible 4) on at least one of the 5 items in the WOMAC Pain Subscale (for the index knee).

5.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

Exclusions Related to OA:

1. Radiologic evidence of severe OA of the knee (Kellgren and Lawrence grade 4) (see Appendix 2)
2. Secondary OA of the index knee (such as septic arthritis, inflammatory joint disease, gout, articular fracture, major dysplasia, congenital abnormality, hemochromatosis)
3. Any other arthritis, included but not limited to RA, psoriatic arthritis, etc.
4. History of pseudo-gout or inflammatory flare-ups
5. History of severe neurological conditions (such as multiple sclerosis, sciatica, fibromyalgia, etc.)
6. Any other chronic pain conditions (e.g., back pain) or disabling conditions affecting the joints
7. Non-ambulatory or requires the use of crutches or a walker
8. Started using a cane within 30 days prior to Screening
9. Worst daily pain (within 24 hours prior to Baseline/FV1) in the contralateral knee assessed as >2 on the 11-point pain NRS scale.

Study Drug-Related Exclusions & Other Medical Conditions

10. Skin disorder present at the study drug application site
11. Presence of contraindications, warnings, or precautions (listed in the Canadian Product Monograph for oral celecoxib) that may put the subject at risk, as assessed by the Investigator
12. Known sensitivity to celecoxib, any NSAID, or menthol
13. History of aspirin-sensitive asthma
14. History of any of the following:
    a. Known coronary artery disease or cerebral artery disease
    b. Coronary artery bypass surgery (CABG) within 1 year prior to Screening
    c. Any other severe or uncontrolled cardiovascular disease, as assessed by the Investigator
    d. Systolic blood pressure (SBP) >149 mmHg and/or diastolic blood pressure (DBP) >94 mmHg at Screening

15. Severe, uncontrolled hepatic, renal, or other systemic disease, as assessed by the Investigator
16. Any malignancy within the previous 5 years, except for superficial skin cancer not on the index knee, cured with local therapy
17. Documented gastroduodenal ulcer or gastrointestinal (GI) bleeding within the last 6 months or presence of other GI disorder that could put the patient at increased risk or interfere with the interpretation of the safety results of the study
18. Uncontrolled diabetes or diabetic neuropathy
19. Psychiatric or psychological conditions that in the opinion of the Investigator may affect the subject's pain assessments (such as depression, anxiety, pain catastrophizing, poor sleep quality)
20. Any of the following abnormal Screening laboratory test results:
    a. serum creatinine ≥ 1.5 times the upper limit of normal (ULN) or Estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2 (Appendix 7);
    b. AST, ALT, or gamma-glutamyl transferase (GGT) ≥ 2 times the ULN;
    c. hemoglobin < 10 g/dL
21. Positive serology for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody at Screening
22. Documented alcohol or other substance abuse within 1 year
23. Body Mass Index (BMI) above 40 kg/m^2
24. Patients who are currently pregnant or planning to be become pregnant or are breast-feeding.

Prohibited Prior, Current, or Planned Treatments:

25. Any history of major surgery to the index knee, minor knee surgery, or injury to the index knee within 1 year prior to Screening
26. Knee arthroscopy (index knee) within 3 months prior to Screening
27. Planned or candidate for knee replacement or knee reconstruction surgery
28. Treatment with or need for any of the following: (1) oral or intramuscular corticosteroids within the past 90 days; (2) intra-articular corticosteroid injection into the index knee within the past 90 days, or into any other joint within the past 30 days; (3) current use of topical corticosteroids on the index knee
29. Received intra-articular viscosupplementation/hyaluronate, joint lavage, or other invasive therapies to the index knee in the past 90 days
30. Prior stable therapy (defined as >3 days per week prior to the Screening) with an opioid analgesic, or anticipated need for opioid analgesic use during the study
31. Use of sedative hypnotic medication, antidepressants with known analgesic effect, antipsychotics, antiepileptics, and anti-Parkinson drugs within the past 14 days

Note: "Known analgesic effect" is defined as any documented evidence of a significant effect on pain outcomes, and is not equivalent to an approved indication or proven efficacy.

32. Regular use of medication for headaches (≥10 days within 30 days prior to Screening)
33. Use of another investigational drug within the previous 30 days or five half-lives of the investigational product, whichever is longer
34. Use of any oral or topical NSAID (apart from the IMP) is prohibited during the study
35. Receipt of a coronavirus 2019 (COVID-19) vaccine within 7 days prior to Screening, or anticipated during the study (between Screening and Week 5).

    Patients who received their first dose of the vaccine may be enrolled as long as their second dose is scheduled later than the planned Week 5 study visit. The dates of the first and second COVID-19 vaccine dose (actual or planned) should be documented in the patient's study file.

Additional Exclusion Criterion Assessed at Baseline/FV1:

36. Non-compliance with the daily diary requirement during the 7-day Screening period (defined as <3 days of daily or nightly pain assessments or <3 days of rescue medication entries).

5.3. Lifestyle Considerations

Patients should abstain from the following during their study participation:

- Smoking / use of tobacco products
- Alcohol and/or recreational drug consumption
- Changes from their routine exercise level (between Screening and the Week 6/EOS visit)

There are no meal or dietary restrictions for study participants.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (date, eligibility criteria failed, or other reason), and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) will not be rescreened.

6. Study Treatment and Concomitant Therapy

Study intervention is defined as any investigational medicinal product (IMP) or non-investigational medicinal product (NIMP) intended to be administered to a study participant according to the study protocol.

G001 (Celecoxib 4% gel for topical administration) and Vehicle gel (placebo) are IMPs in this study. All IMPs are manufactured by Egis Pharmaceuticals PLC, Hungary for Buzzz Pharmaceuticals Limited, Ireland, and will be provided by Bay Area Research Logistics (BARL), Canada to the study sites. G001 and Vehicle may also be referred to as 'study treatment' or 'study drug' in this protocol.

Rescue medication (acetaminophen) used to manage breakthrough pain is considered NIMP in this study and will be supplied locally by the study site (i.e., will not supplied by the Sponsor).

6.1. Overview of the Study Interventions

Study interventions administered during the study are detailed in Table 6.

Table 6 Overview of Study Interventions

Study Arm Name	**Group 1:** G001	**Group 2:** Vehicle	**Groups 1 and 2**
Intervention Name	G001 (Celecoxib Gel 4.0%) [1]	Vehicle (Gel) [1]	Acetaminophen (Rescue medication)
Type	Drug	Drug	Drug
Dose Formulation	Gel for topical administration	Gel for topical administration	Tablet
Unit Dose Strength(s)	G001 (Celecoxib Gel 4.0%), containing celecoxib 40 mg/g [1]	Vehicle Gel, containing no celecoxib [1]	500 mg
Dosage Level(s)	4 grams of the IMP applied to the target knee 4 times daily for 4 weeks	4 grams of the IMP applied to the target knee 4 times daily for 4 weeks	Maximum 500 mg per dose and 2,000 mg/day to manage breakthrough pain [2]
Route of Administration	Topical	Topical	Oral
Use	Experimental (Test)	Placebo (Reference)	Rescue medication
IMP / NIMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided locally by the study site
Packaging and Labeling	The IMP will be provided in 100 gram tubes, labeled as per local	The IMP will be provided in 100 gram tubes, labeled as per local	Commercially available packaging

	requirements [3], packaged according to the randomization scheme [4], and distributed by BARL	requirements [3], packaged according to the randomization scheme [4], and distributed by BARL	

Abbreviations: BARL=Bay Area Research Logistics, Hamilton, ON, Canada; IMP=Investigational Medicinal Product; EOT=End-of-Treatment; FV1=Flare Visit #1; FV2=Flare Visit #2; NIMP=Non-investigational Medicinal Product

[1] Both IMP formulations (G001 and Vehicle) contain menthol 1.5% (added to G001 as solubilizer). The reference product in this study (Vehicle formulation) contains all excipients of G001, but without celecoxib.

[2] Rescue medication use is discouraged, but acetaminophen may be used, as needed, at a dose not exceeding 500 mg per dose and 2,000 mg/day to manage breakthrough pain. No rescue medication use is permitted within 2 hours after each IMP application, and within 12 hours prior to each efficacy assessment (i.e., at the Screening, Baseline/FV1, Week 2, Week 4/EOT, and Week 5/FV2 visits).

[3] The product name, strength, and lot/batch number will be included on each original drug container.

[4] The IMP will be packaged in kit form: 3 x 100g tubes per kit and 12 dosing cards. Each patient will be given 1 kit for each two-week period between visits.

6.2. Study Drug Storage, Handling, Administration, and Accountability

6.2.1. Study Drug Storage and Handling

The Sponsor will supply a sufficient quantity of the study drugs to allow for completion of this study. The IMP will be provided in 100 gram tubes, packaged in kit form: 3 x 100 gram tubes per kit and 12 dosing cards. Each patient will be given 1 kit for each two-week treatment period.

Designated clinical staff will be responsible for monitoring the receipt, storage, and accounting of study drugs according to Good Clinical Practice (GCP).

The IMP is to be transported and stored at room temperature between 15°C and 30°C. Spiking above 40ºC is not permitted. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area under appropriate storage conditions with access limited to authorized/designated unblinded site staff. Any discrepancies/deviations from the above requirements are to be reported and resolved before use of the study drug.

Further details will be provided in the Pharmacy Plan.

6.2.2. Study Drug Dosage and Administration

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or apply study drug. Application of the IMP will occur in accordance with the study-specific Blinding Protocol; see Section 6.3.2.

The first dose will be applied at the clinic, in the presence of a qualified unblinded treatment administrator; subsequent applications will be completed by the patient at the clinic (on Day 15/Week 2 Visit) or at their home (all other applications). Patients will be dispensed a two-week supply of study drug (three tubes of 100 grams) on Day 1 (Baseline/FV1) and on Day 15 (Week 2

Visit), and will be asked to return all unused study drug supplies at the next study visit (Day 15/Week 2 Visit, and Day 29/Week 4/EOT Visit, respectively).

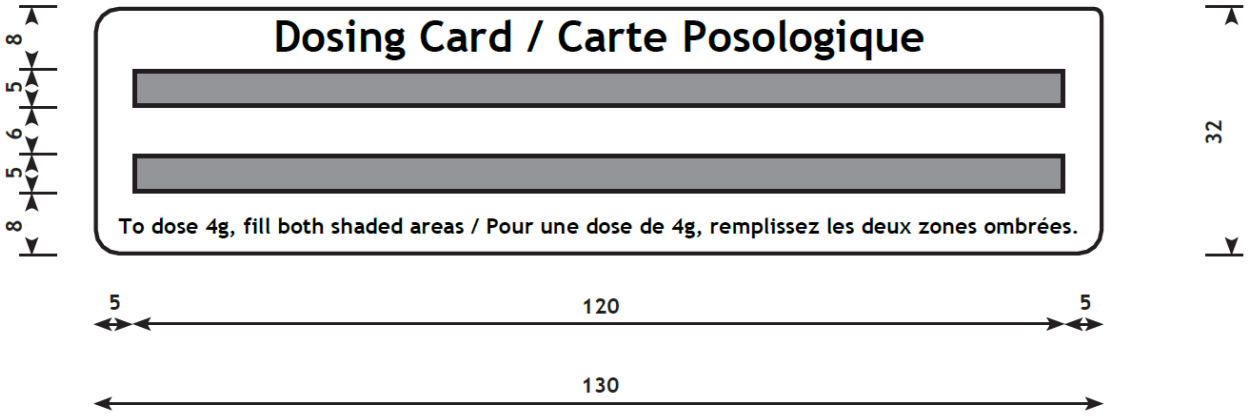
Four grams of the study drug (G001 gel or Vehicle gel) will be applied to the target knee four times daily for four weeks as follows:

- 1st dose between 6 a.m. and 7 a.m.
- 2nd dose: between 11 a.m. and 12 p.m. (~5 hours after the first dose)
- 3rd dose: between 4 p.m. and 5 p.m. (~5 hours after the second dose)
- 4th dose: between 10 p.m. and 11 p.m. (~6 hours after the third dose and shortly after the daily pain assessment)

Note: the first study drug application (Day 1) may occur between 6 a.m. and 8 a.m. Subsequent application times on Day 1 may be modified accordingly, to maintain the ~5-hour interval between consecutive applications.

Accurate dosing will be ensured by using a dosing card; see Figure 2. The dosing card should be used for each application of study drug.

Figure 2 Dosing Card for Study Drug



Patients will be instructed to:

- measure the gel by filling both shaded areas on the dosing card (see Figure 2); then
- using the dosing card, apply the measured amount to the index knee (laterally, medially, and anteriorly: immediately proximal, and ≥4 inches or 10 cm distal to the knee; total application area of ~400 cm^2), and massage it in over at least 1 minute to ensure adequate application over the affected joint;
- replace the cap of the tube tightly after use;
- wait ≥10 minutes before dressing;
- avoid exercise for ≥1 hour before and after application;
- forgo showering/bathing for ≥1 hour after application;
- avoid contact with eyes and mouth;

- wash hands and the dosing card after use;
- store the study drug at room temperature between 15°C and 30°C.

Study treatment will continue for 4 weeks (28 ± 2 days).

6.2.3. Study Drug Accountability

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records) according to GCP.

The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on a drug inventory log.

Unused IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

To avoid bias in the assignment of patients to study treatment, increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatments, treatment allocation in this study will occur through randomization.

Eligible patients with adequate OA pain in the index knee at Baseline/FV1 will be randomly assigned to one of two treatment groups (Group 1: G001; Group 2: Vehicle) in a 1:1 allocation ratio. Randomization will occur centrally, based on a computer-generated randomization schedule, and using an IWRS.

Patients discontinuing the trial after randomization will not be replaced.

6.3.2. Blinding

The Investigator and other study site personnel involved in patient assessments (safety and efficacy), as well as patients will remain blinded to treatment assignment throughout the course of the study. Because a full matching in physical appearance could not be achieved between the experimental and reference formulations (G001 and Vehicle), a separate Blinding Protocol will be in place to ensure that patients and clinic staff involved in assessing the study outcomes remain unaware of the treatment allocation.

To maintain the blind, a third party (such as a designated pharmacist or research nurse), who is not otherwise involved in the patient assessments, will be responsible for the following at the study site:

1) Dispensation of all IMP;
2) Demonstration of the IMP application to each patient prior to their first dose;
3) Oversight of any IMP applications occurring at the clinic;
4) Ensuring that all IMP applications occurring at the clinic are completed individually, in a dedicated area not accessible/visible to other research staff or other patients, and in a consistent manner;
5) Instructing study patients to avoid discussing any physical characteristics (color, transparency, consistency, smell, etc.) of the IMP with the Investigator, other research staff, or other study participants.

The Sponsor and its agents will also be blinded to treatment assignment prior to unblinding of the treatment assignment at the study level, with the exception of select individuals who require access to patient treatment assignments to fulfil their roles during a clinical trial, including those involved in the creation and maintenance of the IWRS and drug dispensation.

Further details are provided in the Blinding Protocol.

6.3.3. Emergency Unblinding

The Investigator will not be provided with the randomization codes. The randomization schedule will be maintained within the IWRS, which has the functionality to allow the Investigator to break the blind for an individual subject.

Under normal circumstances, the blind should not be broken until all subjects have completed the trial and the database is locked.

During the course of the study, the treatment code may only be broken in case of emergency. The Investigator may unblind the treatment assignment for a patient with an SAE if knowledge of treatment assignment will affect the immediate management of the patient. In such case, the Investigator will be able to break the treatment code solely for the patient experiencing the treatment-emergent SAE, within the IWRS. The Investigator is required to consult with the Medical Monitor prior to initiating emergency unblinding. If the SAE requires that an expedited regulatory report be submitted to one or more regulatory agencies (such as in the case of a suspected unexpected serious adverse reaction [SUSAR]), a copy of the report, identifying the patient's treatment assignment, may be sent to investigators in accordance with local regulations.

The Sponsor must be informed of any unblinding (accidental or for emergency reasons) as soon as possible. The date, time, and reason/circumstances for unblinding must be documented in the study file and in the appropriate section of the electronic Case Report Form (eCRF).

Individual unblinding will result in the withdrawal of the patient from the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4. Study Drug Compliance

As described in Section 6.2.2, the first dose of IMP will be applied at the clinic, in the presence of a qualified unblinded treatment administrator; subsequent applications will be made by the patient at the clinic (on Day 15/Week 2 Visit) or at their home (all other applications). Patients will be dispensed two-weeks' supply of IMP (three tubes of 100 grams) on Day 1 (Baseline/FV1) and on Day 15 (Week 2 Visit), and will be asked to return all unused IMP supplies at the next study visit (Day 15/Week 2 Visit, and Day 29/Week 4 Visit, respectively).

The date and time of each dose applied in the clinic will be recorded in the source documents by the qualified unblinded treatment administrator. The date and time of all other doses applied by the patient at home will be recorded on a daily basis in the Treatment Diary. The Investigator (or qualified designee) will contact the patient by phone after one week of treatment (Week 1, study Day 8 ± 1), and after three weeks of treatment (Week 3, study Day 22 ± 1), to verify compliance with the study drug application and daily diary completion requirements. Compliance with IMP applications occurring at home will be assessed at each visit by direct questioning, review of the Treatment Diary entries, and by weighing the unused study drug supplies (tubes) returned by the patient. Results of these compliance checks will be documented in the source documents and eCRF. Deviations from the prescribed dosage regimen should be recorded.

A record of the quantity of IMP dispensed to and used by each patient must be maintained and reconciled with the IMP and compliance records. Study treatment interruptions, delays, and/or skipped doses (including dates) should also be recorded.

Adequate treatment compliance is defined as >80% of the planned doses (i.e., ≥23 out of 28) applied during each week of study treatment.

Inadequate compliance requiring permanent treatment discontinuation is defined as >3 days of consecutive study treatment missed.

6.5. Dose Modifications, Interruptions, and Delays

Patients will be treated according to a standardized dosing regimen consisting of four grams of the study drug (G001 or Vehicle gel) applied to the index knee four times daily (for a total daily dose of 16 grams) administered over four weeks.

No dose modifications are planned for this study. However, in certain situations (e.g., moderate or severe local application site reactions; see description in Section 11.6.4), dosing may be interrupted until the event subsides or returns to tolerable levels. Patients should be instructed to contact the Investigator (or research staff) should they experience an AE that requires interruption of study treatment. Patients requiring treatment interruption lasting >3 consecutive days will have their study treatment permanently discontinued.

6.6. Continued Access to Study Intervention after the End of the Study

Currently, the Sponsor does not plan to provide G001 to patients who have completed the study.

6.7. Treatment of Overdose

The low systemic absorption of G001 renders overdose very unlikely.

However, undesirable effects similar to those observed following an overdose of celecoxib tablets can be expected if G001 is inadvertently ingested (1 unit of 100 grams of G001 contains the equivalent of 4 grams of celecoxib).

Oral celecoxib (Celebrex) doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose (Celebrex CPM 2022).

In the event of accidental ingestion, patients should be managed by symptomatic and supportive care. There are no specific antidotes. Based on the high degree of plasma protein binding (>97%) hemodialysis, forced diuresis, alkalinization of urine, or hemoperfusion are unlikely to be useful in celecoxib overdose. Emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (Celebrex CPM 2022).

In the unlikely event of an overdose, apart from adequate patient management (as described above), the Investigator should: (1) contact the Medical Monitor immediately; (2) document the overdose, including the quantity of the excess dose; (3) consider withdrawal of the patient from the study.

6.8. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, route of administration, and frequency

6.8.1. Prohibited Medication and Interventions

Patients taking any opioid analgesics > 3 days per week for the previous month before Screening will be excluded from the study. Patients on other opioid or other analgesic regimens may only be enrolled if their analgesic treatment may be safely discontinued by/at the Screening Visit. Prior NSAID and acetaminophen use will be discontinued at the Screening Visit to allow for washout and symptom flare. Acetaminophen may be used as rescue medication only (as described in Section 6.8.3). Any non-prescription or prescription analgesics (including NSAIDs, cyclooxygenase II-inhibitors, etc.) other than the IMP and the allowed amount of rescue medication (acetaminophen) are prohibited up to and including the Week 5/FV2 visit.

Corticosteroids should not be taken during the trial or within the following timelines prior to Screening: (1) oral or intramuscular corticosteroids within the past 90 days; (2) intra-articular corticosteroid injection into the index knee within the past 90 days, or into any other joint within the past 30 days; (3) use of topical corticosteroids on the index knee must be discontinued by/at the Screening Visit.

Use of sedative hypnotic medication, anti-depressants with known analgesic effect, antipsychotics, antiepileptics, and anti-Parkinson drugs is prohibited within 14 days prior to Screening and during the study. "Known analgesic effect" is defined as any documented evidence of a significant effect on pain outcomes, and is not equivalent to an approved indication or proven efficacy.

Refer to Table 7 for further details on prohibited medication and treatments, including minimum washout/treatment-free periods.

Table 7 Prohibited Medication and Treatments

Prior Surgeries & Other Interventions	**Minimum Treatment-Free Interval Prior to the Screening Visit**
Any major surgery to the index knee Minor surgery (or injury) to the index knee	Lifetime 12 months
Knee arthroscopy (index knee)	3 months (90 days)
Oral or intramuscular corticosteroids Intra-articular corticosteroid injection into the index knee Intra-articular corticosteroid injection into any other joint Topical corticosteroid use on the index knee	3 months (90 days) 3 months (90 days) 1 month (30 days) 0 days [1]
Intra-articular viscosupplementation/hyaluronic acid, joint lavage, or other invasive therapies to the index knee	3 months (90 days)
Prohibited Medication/Class	**Minimum Washout Period Prior to the Screening Visit**
Any investigational drug/therapy	1 month (30 days)
Hypnotics and Sedatives [2], Antipsychotics / Neuroleptics [3], Antidepressants with known analgesic effect [4], Antiepileptics [5], and Anti-Parkinson drugs [6]	2 weeks (14 days)
Opioid analgesics [7]	[5]
Any oral and topical NSAIDs (apart from the IMP), and any other non-opioid analgesic medication apart from protocol-permitted rescue medication use	0 days [8]
Receipt of a COVID-19 vaccine	7 days

Abbreviations: IMP=Investigational Medicinal Product; NSAID=nonsteroidal anti-inflammatory drug

[1] Topical corticosteroid use

[2] Anatomical Therapeutic Chemical (ATC) Classification, Pharmacological Subgroup N05C

[3] ATC Classification, Pharmacological Subgroup N05A

[4] ATC Classification, Pharmacological Subgroup N06A. "Known analgesic effect" is defined as any documented evidence of a significant effect on pain outcomes, and is not equivalent to an approved indication or proven efficacy.

[5] ATC Classification, Therapeutic Subgroup N03

[6] ATC Classification, Therapeutic Subgroup N04

[7] ATC Classification, Pharmacological Subgroup N02A. Prior use of opioid analgesics > 3 days per week for the previous month prior to the Screening visit is exclusionary, and any opioid analgesic use during the study is prohibited.

[8] All analgesic medication use (apart from protocol-permitted rescue medication) must be discontinued at Screening.

The use of non-pharmacological pain management modalities (Transcutaneous Electrical Nerve Stimulation, acupuncture, and other interventional adjunctive therapy, physiotherapy, packs, massages), naturopathic treatments and remedies will be prohibited up to and including the Week 5/FV2 visit.

The potential effect of the available coronavirus 2019 (COVID-19) vaccines on the safety or efficacy of COX-inhibitors or on existing inflammatory conditions is currently unknown. However, there is published evidence suggesting that NSAIDs dampen the body's antibody and cytokine response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vaccine (Chen et al. 2021). Furthermore, in clinical trials of COVID-19 vaccines approved for use in Canada, after the first and second doses of the vaccines, the incidence of arthralgia (reported as an adverse effect) was up to 28% and up to 45.5%, respectively, and the frequency of antipyretic or pain medication use was up to 28%, and up to 57%, respectively (COVID-19 Vaccine Moderna Product Monograph [PM], 2021; Pfizer-BioNTech COVID-19 Vaccine PM, 2021; AstraZeneca COVID-19 Vaccine PM, 2021; Janssen COVID-19 Vaccine PM, 2021). A similar frequency of adverse pain effects and concomitant analgesic use would have a significant impact on the safety and efficacy assessments in the current study, and therefore the integrity of the study overall. Given the above considerations, receipt of a COVID-19 vaccine will be prohibited during the study.

The Medical Monitor should be contacted if there are any questions regarding medications and interventions.

6.8.2. Exceptions to Prohibited Medication and Interventions

Low-dose acetyl salicylic acid (ASA, aspirin) at oral doses ≤81 mg per day may be continued for cardiovascular prophylaxis.

6.8.3. Rescue/Breakthrough Pain Medicine

Rescue medication use is discouraged, but acetaminophen may be used, as needed, at a dose not exceeding 500 mg per dose and 2,000 mg/day to manage breakthrough pain. No rescue medication use is permitted within 2 hours after each IMP application, and within 12 hours prior to each efficacy assessment (i.e., at the Screening, Baseline/FV1, Week 2, Week 4/EOT, and Week 5/FV2 visits). Acetaminophen may only be used as rescue medication during the study.

Patients will be given a study diary and instructed to enter any breakthrough pain medication (acetaminophen) use on a daily basis. The reason for taking rescue medication (such as for OA pain or another pain condition) will also be recorded in the daily diary and in the eCRF.

Rescue medication (acetaminophen) used to manage breakthrough pain is considered NIMP in this study and will be supplied locally by the study site (i.e., will not supplied by the Sponsor).

7. Discontinuation of Study Drug and Patient Withdrawal

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue study treatment. Reasons for permanent discontinuation of study treatment may include any of the following:

- Interruption of study treatment for >3 consecutive days (e.g., due to an AE or other reason)
- Any medical condition that prevents the patient from safely completing the study
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of/requirement for prohibited medication
- Patient non-compliance with the study treatment or assessments, as determined by the Investigator or the Sponsor
- Pregnancy
- Patient's decision / withdrawal of consent

If study treatment is permanently discontinued for reasons other than withdrawal of consent from all further study participation, the patient will remain in the study, and will be asked to complete the EOT assessments (within no later than 2 days after the last dose of IMP), and the EOS assessments (within 14 ± 3 days after the last IMP application). See the SoA (Section 1.3) for data to be collected at these visits.

The primary reason for permanent study drug discontinuation must be recorded in the eCRF. In case the reason is patient decision / withdrawal of consent, the patient's willingness, or refusal to undergo further assessments (safety with/without efficacy assessments) should be recorded in the eCRF.

7.1.1. Liver Chemistry Stopping Criteria

As a standard precautionary measure, in case of:

(1) ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or

(2) ALT or AST ≥3 × ULN and INR >1.5,

which may indicate severe liver injury (possible Hy's Law), regardless of the causality assessment of the event, the Medical Monitor must be notified in an expedited manner, and permanent discontinuation of study treatment may be considered.

7.2. Patient Withdrawal from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the Investigator has the right to withdraw a patient from the study at any time.

Reasons for patient withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent

- AE
- Loss to follow-up
- Patient non-compliance with the study treatment or assessments
- Study termination or site closure

At the time of premature discontinuation, if feasible, an EOT should be conducted, followed by an EOS visit, as shown in the SoA (Section 1.3).

The patient will be permanently discontinued both from the study treatment and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request (verbally or in writing) destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow up

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

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is described in Section 10.4.1.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form (ICF) may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

8.1. Screening Assessments and Activities

8.1.1. Informed Consent Form and Screening Logs

Written informed consent for participation in the study must be obtained before performing any study-specific screening test or procedure. Signed ICFs for randomized patients and for patients who are not subsequently randomized (screening failures) must be maintained at the study site; refer to Section 10.1.2 for details.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The Investigator (or qualified designee) will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1.2. Demographic Data, General Medical and Disease History and Prior/Concomitant Medications

Demographic data include age, gender, and self-reported race and ethnicity.

Medical history includes OA history (date of diagnosis, prior treatment), general medical history, surgical history, and reproductive status. Documented diagnosis of OA of the knee, meeting ACR criteria for classification of idiopathic (primary) OA (see Appendix 1) for at least 6 months prior to Screening is required for enrolment.

Medication history includes pharmacological treatment (oral, parenteral, or topical; prescription and non-prescription) in the past 90 days, with focus on medications used for the management of OA and prohibited medications; see Section 6.8.1.

Concomitant medications include all medications (e.g., prescription and non-prescription drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient at the time of the Screening Visit or any time during the study.

8.1.3. Weight and Height Measurements

The patient's body weight and height will be measured, and BMI calculated by dividing the patient's weight in kilograms by the square of his/her height in meters.

8.1.4. Screening Serology

At the Screening Visit only, patients will be tested for HIV antibody, HBsAg, or HCV antibody; see Appendix 5. Patients with positive serology test results (any of the three parameters) will be excluded from the study.

8.1.5. Radiological Examination

Patients will undergo conventional radiological (X-ray) examination of the index knee during Screening. Exemptions include patients who:

(1) had an X-ray of the index knee completed within 3 months prior to the Screening visit, and

(2) received no treatment since that may have altered the radiological findings, including OA grade.

Review and interpretation of radiographic images will be the responsibility of the Investigator.

Radiologic evidence of OA in the index knee of grade 2 (mild) or grade 3 (moderate) according to Kellgren and Lawrence Radiographic Grading (see Appendix 2) is required for enrolment.

8.1.6. Worst Daily Pain Assessment (11-point Pain NRS)

The pain NRS is an ordinal 11-point Likert scale, with scores ranging from 0 (no pain) to 10 (worst possible pain).

Worst daily pain (24-hour recall) will be assessed for both knees at the Screening and Baseline/FV1 visits using the 11-point pain NRS.

The worst daily pain score (within 24 hours prior to Screening and Baseline/FV1) in the index knee must be between 4 and 8 on the 11-point pain NRS for eligibility.

The worst daily pain score (within 24 hours prior to Baseline/FV1) in the contralateral knee must be ≤2 on the 11-point pain NRS scale for continued eligibility.

8.1.7. Screening Diary

Patients will be given a Screening Diary and instructed to enter the following on a daily basis during the 7-day Screening period:

- Between 6 a.m. and 7 a.m., patients should rate their worst pain intensity from the previous ~8 hours (night-time pain) in the index knee on the 11-point pain NRS;
- Between 10 p.m. and 11 p.m., patients should rate their worst pain intensity from the previous ~16 hours (daytime pain) in the index knee on the 11-point pain NRS, and enter any breakthrough pain medication (acetaminophen) use during the day.

Diary entries made during the Screening period will be reviewed at the Baseline/FV1 visit.

8.1.8. Other Screening Assessments

Other assessments completed at the Screening Visit are as follows:

- WOMAC Index (see Section 8.2.1);
- PGA and IGA of disease activity (see Section 8.2.2);
- Physical examination (see Section 8.3.1);
- Vital signs measurements (see Section 8.3.2);
- Standard 12-lead ECG (see Section 8.3.3);
- Safety Laboratory Testing* (see Section 8.3.4 and Appendix 5)
- Urine pregnancy test (see Section 8.3.5);
- Urine drug screen (see Section 8.3.6);
- AE recording (see Section 8.4 and Appendix 6)

* Note: For confirmation of eligibility, a screening laboratory test may only be repeated in case of a strictly borderline value. The Screening period may be extended by up to 2 days solely to obtain the repeat laboratory result, as long as there are adequate daily diary entries (minimum of 3 days preceding the baseline visit), and the patient continues to meet all other enrolment criteria.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. WOMAC OA Index

In this study, patients will complete the WOMAC OA Index in person at the Screening, Baseline/FV1, Week 2, Week 4/EOT, and the Week 5/FV2 visit; see SoA (Section 1.3). The WOMAC® 3.1 Index in 5-point Likert format will be used in this study; see Appendix 3.

The WOMAC OA index is a self-administered questionnaire assessing three dimensions of pain, disability and joint stiffness in knee and hip OA using a battery of 24 questions (Bellamy et al. 1988):

- Pain subscale (5 items): during walking, using stairs, in bed, sitting or lying, and standing
- Stiffness subscale (2 items): after first waking and later in the day
- Physical Function subscale (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

The Likert version of the WOMAC is rated on an ordinal scale of 0 to 4, where 0 means the lowest level of symptoms or physical disability:

- 0=none
- 1=mild
- 2=moderate

- 3=severe
- 4=extreme

The WOMAC takes approximately 12 minutes to complete.

For each subscale, the scores for individual items are summed, providing the following possible ranges: 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function. The sum of the three subscales provide a maximum total score of 96 (McConnell et al. 2001). Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

8.2.1.1. Standardization of Assessments

Even though the WOMAC measure has been used for decades (Bellamy et al. 1992) and is one of the most commonly used outcome measures in knee OA research (Kersten et al. 2010; Collins et al. 2011), different versions of the WOMAC measure exist, and there is variation in how the WOMAC outcome score is collected (5-level Likert scale, 11-point NRS, or 100 mm VAS), calculated (for example, using the total or average of the items) (Copsey et al. 2019), and reported (Woolacott et al. 2012). A lack of clarity and consistency in the use and scoring of an instrument can hinder the interpretation of study results (Copsey et al. 2019). Therefore, to standardize the use of the WOMAC Index across the study, guidance for minimizing bias will be provided through applicable training for site staff.

8.2.2. Global Assessments of Disease Activity

Patient and Investigator Global Assessment (PGA and IGA) of disease activity evaluate OA in the in the index knee over the last 48 hours on a 5-point Likert scale, where:

- 0=very good
- 1=good
- 2=fair
- 3=poor and
- 4=very poor

8.2.3. Global Assessments of Treatment Benefit

Patient and Investigator Global Assessment (PGA and IGA) of treatment benefit will be completed using a 5-point Likert scale (0=very good; 1=good; 2=fair; 3=poor; and 4=very poor) after two (2) and four (4) weeks of treatment; see SoA.

8.2.4. Treatment Diary

Randomized patients will be given a Treatment diary at the Baseline/FV1 visit (after randomization) and instructed to enter the following on a daily basis through the Week 4/EOT Visit:

- Between 6 a.m. and 7 a.m. (before the first daily study drug application), patients should rate their worst pain intensity from previous ~8 hours (nighttime pain) in the index knee on the 11-point pain NRS;
- During the day: patients should enter the time of each study drug application;

- Between 10 p.m. and 11 p.m. (before the last daily study drug application), patients should rate their worse pain intensity from previous ~16 hours (daytime pain) in the index knee on the 11-point pain NRS, and enter any AE experienced, and rescue medication used during the past day.

Between Week 4/EOT Visit and the Week 5/FV2 Visit, patients will be asked to enter the following in their Treatment diary on a daily basis:

- Between 6 a.m. and 7 a.m., patients should rate their worst pain intensity from previous ~8 hours (nighttime pain) in the index knee on the 11-point pain NRS;
- Between 10 p.m. and 11 p.m., patients should rate their worse pain intensity from previous ~16 hours (daytime pain) in the index knee on the 11-point pain NRS, and enter any AE experienced, and rescue medication used during the past day.

Treatment diary entries will be reviewed by the clinical staff over the phone during the Week 1 and Week 3 safety and compliance follow-up call, and in person at the Week 2, Week 4/EOT, and Week 5/FV2 visits. Any compliance issues will be addressed with the patient.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

The Investigator or qualified health care provider designee will perform a complete physical examination at Screening and Week 4/EOT, and a brief, symptom-driven examination at Week 6/EOS.

A complete physical examination will be performed with special attention to the cardiovascular, gastrointestinal (GI), and musculoskeletal systems, as well as skin and subcutaneous tissues. Investigators may use medical judgment to determine the need for evaluating the breast, genital, and anorectal areas at each applicable study visit.

8.3.2. Vital Signs Measurements

Vital signs measurements will include blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature.

Vital signs should be taken before blood collection for laboratory tests.

Blood pressure and pulse (HR) measurements will be assessed with the patient in a sitting position, after 3 minutes of rest, with a completely automated device. Manual techniques will be used only if an automated device is not available. Two consecutive BP readings (at least 1 minute apart) will be recorded, and the average of the two readings will be entered in the eCRF.

8.3.3. Electrocardiograms

A single standard 12-lead ECG recording will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that measures PR, QRS, QT interval, and automatically calculates the heart rate and QTc interval.

8.3.4. Clinical Safety Laboratory Assessments

Refer to Appendix 5 for the list of clinical safety laboratory tests (hematology, blood chemistry, and urinalysis) to be performed and to the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory tests, as defined in Appendix 5, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

The Investigator must review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline level or are no longer considered clinically significant by the Investigator or Medical Monitor. If clinically significant values do not return to normal/Baseline level within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Medical Monitor notified.

8.3.5. Pregnancy Testing

All women of childbearing potential will undergo repeat urine human chorionic gonadotropin (hCG) pregnancy tests during the study, as outlined in the SoA (Section 1.3) and in Appendix 5. If a urine pregnancy test is positive, it must be confirmed by a serum hCG pregnancy test.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 24 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the Investigator (e.g., Müllerian agenesis).

Patients with a positive pregnancy test during Screening will be excluded from the study. Patients with a positive pregnancy test during the treatment or post-treatment follow-up period will be withdrawn from the study.

8.3.6. Urine Drug Screen

Urine drug screen will include amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, phencyclidine, and a panel of tricyclic antidepressants.

8.3.7. Skin Irritation Test

Skin irritation will be assessed by the Investigator using the Berger/Bowman Scoring Scale (Berger and Bowman, 1982; US FDA Guidance 2018b), comprised of the 'Dermal Response' and 'Other Effects' scoring system, as outlined in Appendix 4. To the extent feasible, the same scorer should complete all three skin irritation assessments (Week 2, Week 4/EOT, and Week 6/EOS) for a patient.

'Dermal Response' is evaluated on an 8-point scale (0=No evidence of irritation; 1=Minimal erythema that is barely perceptible; 2=Definite erythema that is readily visible and minimal edema

or minimal papular response; 3=Erythema and papules; 4=Definite edema; 5=Erythema, edema, and papules; 6=Vesicular eruption; 7=Strong reaction spreading beyond the application site).

'Other Effects' scores are reported as a number and letter combination: A (0)=Slightly glazed appearance; B (1)=Marked glazed appearance; C (2)=Glazing with peeling and cracking; F (3)=Glazing with fissures; G (3)=Film of dried serous exudates covering all or part of the application site; H (3)=Small petechial erosions and/or scabs.

The sum of the 'Dermal Response' and the numeric equivalent of the 'Other Effects' provides the Numerical Total Score. Refer to Appendix 4 for details.

8.4. Adverse Events, Serious Adverse Event, and Other Safety Reporting

The definitions of AEs and SAEs, method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs and SAEs; see Section 8.4.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs occurring between the Screening Visit and the Week 6/EOS Visit, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

All SAEs will be recorded and reported to the to the Pharmacovigilance (PV) and Safety Manager immediately and under no circumstance later than within 24 hours after learning about the event, as described in Appendix 6. The Investigator will submit any updated SAE data to the to the PV and Safety Manager within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the patient's study participation. However, if the Investigator learns of any SAE (fatal or non-fatal), at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

The Investigator should proactively follow each AE/SAE until the event has resolved to Baseline level or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up (as defined in Section 7.3), or the patient withdraws consent (as described in Section 7.2).

Every effort should be made to follow all SAEs considered to be related to the study drug until a final outcome can be reported. Further information on follow-up procedures is provided in Appendix 6.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor (or designee) of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Research Ethics Boards (REB), and investigators. This will include preparation and expedited submission of safety reports for SUSARs according to local regulatory requirements.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., SUSAR, or summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/REB, if appropriate according to local requirements.

8.4.5. Pregnancy

In the unlikely event of a pregnancy occurring during the study, the Investigator will record pregnancy information on the appropriate Pregnancy Reporting Form and submit it to the PV and Safety Manager within 24 hours of learning of the pregnancy, as described in Appendix 6.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported as such.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor.

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

8.4.6. Disease-Related Events Not Qualifying as AEs

Worsening of the underlying condition (OA) and lack of efficacy will not be reported as AEs in this study.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest for G001 include:

- Application site adverse reactions.

9. Statistical Considerations

This is a double-blind, randomized, parallel-group, vehicle-controlled study to evaluate the efficacy, safety, and local tolerability of G001 compared to Vehicle in patients with symptomatic OA of the knee.

Eligible patients will be randomly assigned to one of two treatment groups (G001 or Vehicle) in a 1:1 allocation ratio.

The primary outcome will be the change from Baseline in the WOMAC Pain Subscale rating at the Week 4/EOT visit.

9.1. Sample Size Determination

A total sample size of 174 evaluable patients (87 per group) achieves 80% power to detect a difference between treatment groups analysed using a t-test and a significance level (alpha) of 0.05. The assumed difference in group means from Vehicle control under the alternative hypothesis is 1.5 points in the WOMAC Likert Pain Subscale (0-20 scale). The common SD is assumed to be 3.5. This sample size calculation was performed using PASS 2020 v20.0.1.

The assumptions on change in WOMAC pain score were selected based on available literature on clinically relevant differences and efficacy of celecoxib oral formulation (see Sections 2.2.1 and 4.3.1).

Based on available literature, it is estimated that up to 20% of patients may withdraw from the study prior to the Week 4 efficacy assessment. Therefore, to control for possible dropouts, the sample size is increased to 210, or 105 per treatment arm.

9.2. Analysis Sets

Analyses will be performed based on the following datasets:

- Modified Intent-to-Treat Population (mITT): The mITT will include all randomized patients who received at least one dose of study drug and provided both Baseline/FV1 and Week 4/EOT efficacy assessments. The mITT population will be the primary analysis population for the assessment of efficacy.
- Per Protocol (PP) Population: The PP population will include all patients in the mITT population who completed the study without major protocol deviations that could impact the assessment of efficacy. The primary and secondary efficacy analyses will also be completed on the PP population. The list of major protocol deviations requiring exclusion from the PP Population will be finalized prior to the clinical database lock and unblinding.
- Safety Population: The Safety population will include all randomized patients who received any amount of study drug. The Safety Population will be used for all safety analyses only.

For all efficacy analyses (based on the mITT and the PP populations), patients will be grouped according to the treatment assigned at randomization. For all safety analyses, patients will be grouped according to the treatment actually received.

9.3. Statistical Analyses

This section is a summary of the planned statistical analyses for the protocol. A Statistical Analysis Plan (SAP) will be prepared and finalized prior to DBL and will include a full technical and detailed description of the statistical analyses described in this section.

9.3.1. General Considerations

All data collected will be documented using summary tables, figures, and/or patient data listings presented by treatment group. For continuous variables, descriptive statistics (number (n), mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented.

Patient disposition, study drug exposure, reasons for study drug discontinuation and withdrawals from the study will be summarized, as will demographic variables such as age, sex, race/ethnicity, and other relevant baseline characteristics.

All major protocol deviations will be summarized and reported.

Unless otherwise specified, the baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

9.3.2. Primary Endpoint

The primary outcome will be the change from Baseline in the WOMAC Pain Subscale rating at the Week 4/EOT visit. The WOMAC will be scored according to the WOMAC® 3.1 User Guide XI. The maximum WOMAC Pain Subscale rating is 20, and higher scores indicate worse pain; refer to Section 8.2.1 and Appendix 3 for details.

While every effort will be made to avoid partially completed assessments, missing data will be handled as instructed in the WOMAC® 3.1 User Guide XI. If two or more pain questions are missing an answer, the pain subscale will not be scored and will be considered missing. If only one question was not answered, the average value for the subscale from the remaining answers will be assigned for the missing question. There will be no imputation for entirely missing pain subscales scores.

The primary analysis will be performed using an analysis of covariance (ANCOVA) model, to compute the t-test for the difference between group means adjusted for Baseline WOMAC Pain Subscale score. The model will include treatment as the independent variable, change from Baseline at the Week 4/EOT visit as the outcome variable, and Baseline WOMAC Pain Subscale score as a covariate. Statistical significance will be assessed using a significance level of 0.05.

The primary endpoint will be assessed in the mITT population as primary, with no imputation for missing data (apart from missing data handled as instructed in the WOMAC® 3.1 User Guide XI, as described above), and in the PP population as supportive. Additional sensitivity analysis of the primary endpoint, including a completers analysis, where subjects who discontinued prior to Week 4 are excluded, may be performed, and will be further described in the SAP. WOMAC Pain Subscale scores will also be displayed graphically.

9.3.3. Secondary Endpoints

A complete list of secondary endpoints is provided in Section 3 (Table 5).

Analysis of secondary endpoints will be considered supportive analysis. Hence, no p-value adjustment will be made for multiple endpoints or multiple comparisons in the secondary efficacy analysis.

9.3.3.1. WOMAC Physical Function and Stiffness Subscale and Total Scores

The analysis of secondary efficacy endpoints of WOMAC Physical Function Subscale, WOMAC Stiffness Subscale and WOMAC Total Score will be consistent with that described for the primary endpoint. Refer to Section 8.2.1 and Appendix 3 for additional details on these scales.

Missing data will be handled as suggested in the WOMAC® 3.1 User Guide XI, with further details described in the SAP. Scores will also be displayed graphically.

9.3.3.2. Weekly Mean Worst Daily and Nightly Pain NRS Scores

Baseline worst *daytime* and worst *nighttime* pain severity scores will be calculated as the mean worst *daytime* or worst *nighttime* pain NRS scores from the screening diary entries (3-7 days prior to Baseline/FV1).

The mean worst *daytime* pain severity scores at Week 4/EOT will be calculated as the sum of the worst *daytime* pain 11-point NRS scores for the last 7 days of the treatment period (e.g., from Day 22 through Day 29), divided by the number of worst *daytime* pain assessments during this 7-day period.

The mean worst *nighttime* pain severity scores at Week 4/EOT will be calculated as the sum of the worst *nighttime* pain 11-point NRS scores for the last 7 days of the treatment period (e.g., from Day 22 through Day 29), divided by the number of worst *nighttime* pain assessments during this 7-day period.

The average worst *daytime* and *nighttime* pain severity scores at the Week 5/FV2 visit will be calculated as the sum of the worst *daytime* or *nighttime* pain scores for the post-treatment period (i.e., between the Week 4/EOT and Week 5/FV2 visits) and divided by the number of days of post-treatment follow-up.

Weekly mean worst *daytime* and *nighttime* pain NRS scores will be presented by treatment group. Changes from baseline in average worst *daytime* and in average worst *nighttime* pain severity scores at Week 4/EOT in the two treatment groups will be compared using a t-test. Percentages of patients achieving ≥20%, ≥30% and ≥50% reduction from Baseline in worst *daytime* pain and in worst *nighttime* pain severity scores (11-point pain NRS) at Week 4/EOT will also be presented by treatment group.

NRS scores will also be displayed graphically.

9.3.3.3. Global Assessments of Disease Activity and Overall Treatment Benefit

For PGA and IGA of disease activity, patients will be classified according to the following three categories:

- "Improved" (defined as a reduction of 2 grades or more from Baseline for grades 2 through 4 or a change in grade from 1 to 0);
- "Worsened" (defined as an increase of 2 or more grades from Baseline for grades 0 through 2 or a change in grade from 3 to 4); or
- “No change” (remaining patients).

The categorical responses will be presented by treatment and visit. A logistic regression model may be used to assess between group differences, including baseline disease activity as a covariate, with further details described in the SAP.

In addition, at the Week 4/EOT visit, patients will provide an overall assessment of treatment benefit using the same 5-point Likert scale (0=very good; 1=good; 2=fair; 3=poor; and 4=very poor). The distribution of overall treatment benefit scores will be presented descriptively, by treatment group.

9.3.3.4. Rescue Medication Use

The number and percentage of subjects with any rescue medication (acetaminophen) use will be presented, along with number of rescue doses, total daily dose, and the percentage of days with any rescue medication use during the last week of study treatment, and overall during the study treatment period (between the first and last dose dates).

9.3.4. Subgroup Analyses of Efficacy Endpoints

Subgroup analyses of primary and select secondary endpoints may be performed based on prior OA treatment (pre-study NSAID or acetaminophen use only) depending on the number of patients in each category.

9.3.5. Safety Analyses

Adverse events (AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) and presented by System Organ Class (SOC) and Preferred Term for each treatment group. Additional displays will highlight the Investigator-rated severity and relationship to study treatment as well as serious adverse events (SAEs), AEs leading to withdrawal of treatment, and application site AEs.

Laboratory parameters (and changes from Baseline in these parameters) will be summarized. In addition, shift changes from Baseline in categories (normal, low, high, missing) will be presented by treatment group across the visits. Clinically relevant laboratory abnormalities will be recorded as AEs.

Vital signs measurements (and changes from Baseline in these measurements) will be summarized by mean values (with SD), medians, and range. Clinically relevant changes in vital signs will be recorded as AEs.

Clinically relevant abnormal physical examination findings will be recorded as medical history at Baseline/FV1 (prior to the first dose in study treatment), and as AEs if detected after the first dose of study treatment.

9.3.6. Analysis of Skin Irritation

Skin irritation will be assessed using the Berger/Bowman Scoring Scale (Berger and Bowman, 1982; US FDA Guidance 2018b), as described in Section 8.3.7. The Total Skin Irritation Score will be calculated as the sum of the 'Dermal Response' and the numeric equivalent of the 'Other Effects'; see Appendix 4.

Descriptive statistics for the numerical Total Skin Irritation Scores as well as the Dermal Response and Other Effects sub-scores will be presented by treatment group and visit.

If a patient was removed from treatment due to skin irritation, the patient's skin irritation score at the time of treatment discontinuation will be imputed at subsequent assessment time-point(s) (last observation carried forward [LOCF]). If a patient was removed from treatment due to reasons other than skin irritation, missing data will not be imputed.

9.4. Interim Analysis

No interim analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, October 2013) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) GCP Guidelines
- All applicable laws and regulations.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants. A Clinical Trial Application (CTA) for the study will be submitted to Health Canada and the study drug will not be initiated unless an appropriate 'No Objection Letter' has been received. A CTA notification will be provided to Health Canada upon completion of the study or at study termination.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., patient recruitment materials) must be submitted to an IRB/REB by the Investigator and reviewed and approved by the IRB/REB before the study is initiated. IRB/REB notifications and approvals should be filed in the study file, with a copy provided to the Sponsor.

Any amendments to the protocol will require IRB/REB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing oversight of the conduct of the study at the site and adherence to requirements set out by the ICH guidelines, the IRB/REB, and all other applicable local regulations
- Providing written summaries of the status of the study to the IRB/REB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/REB
- In addition to the requirements for reporting all SAEs to the Sponsor, investigators must comply with requirements for reporting SAEs or other significant safety findings to the IRB/REB as required by IRB/REB procedures.

10.1.1. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10.1.2. Informed Consent Process

Written informed consent for participation in the study must be obtained before performing any study-specific screening test or procedure.

The Investigator or his/her representative will explain the nature of the study to the prospective study participant and answer all questions regarding the study.

Patients must be informed that their participation in the study is voluntary. Patients will be required to sign the study ICF that meets the requirements of local regulations, ICH guidelines, and the reviewing IRB/REB. The authorized person obtaining the informed consent must also sign the ICF. Signed ICFs for randomized patients and for patients who are not subsequently randomized (screening failures) must be maintained at the study site and must be available for verification by study monitors at any time. A copy of the signed ICF must be provided to the patient.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

In case the ICF is amended, patients must be re-consented to the most current version of the ICF during their participation in the study.

10.1.3. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF signed by the patient, unless otherwise required by law. Patient must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the ICF.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/REB for each study site, as appropriate. Patients must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/REB members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

The Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, in clinical trial registries (such as www.ClinTrials.gov).

10.2. Data Collection and Management

10.2.1. Data Quality Assurance

A contract research organization (CRO; Veristat Inc., Canada) will be responsible for the data management of this study, including quality checking of the data. Data will be collected via electronic data capture (EDC) through use of eCRFs. Sites will be responsible for data entry into

the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce eCRF Specifications for the study, including quality checking to be performed on the data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored and records retention for the study data will be consistent with the CRO's SOPs.

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact patient safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report (CSR).

10.2.2. Electronic Case Report Forms

All patient data relating to the study will be recorded on eCRF unless transmitted to the CRO electronically (e.g., laboratory data). Secure portals are used to transfer data to Data Management by the Central Laboratory.

IBM® Clinical Development, a validated United States (U.S.) Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 compliant eCRF system will be used to capture data for the study. The eCRF will be designed to capture the data according to the protocol, Sponsor requirements and Clinical Data Interchange Standards Consortium (CDISC) Clinical Data Acquisition Standards Harmonization (CDASH) guidelines.

All eCRFs should be completed by designated, trained site staff. Guidance on completion of eCRFs will be provided. The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

At the end of the study, the Investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the patient data will be required.

10.2.3. Patient and Clinician-Reported Outcome Data

Patient-reported outcome data not included in the daily diary, and clinician-reported outcome data are being collected through use of appropriate paper forms provided by the clinical CRO (Veristat) and transferred to the EDC by site staff.

10.2.4. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

Source documents (paper or electronic) are files in which patient data are originally (for the first time) recorded and documented. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, and

laboratories involved in a clinical trial. Before study initiation, the types of source documents that are to be generated will be clearly defined in the Monitoring Plan.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, as applicable. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the requirements for retention of records described in Section 10.2.5.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.2.5. Record Retention

Records and documents pertaining to the conduct of this study and the distribution of IMP, including signed ICFs, eCRFs, laboratory test results, and medication inventory records, must be retained by the Investigator for 15 years after study completion. After that period of time, the documents may be destroyed. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.3. Study Documentation and Monitoring

10.3.1. Study Documentation

The Investigator must maintain files of essential documents as defined by the ICH GCP guidelines and local requirements to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/REB and governmental approval.

The Investigator’s site file must be available at monitoring visits and during an audit or inspection.

In addition, at the end of the study, the Investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

10.3.2. Site Inspections and Monitoring

Site visits will be conducted by the Sponsor or an authorized CRO representative for inspection of study data, patients' medical records, and eCRFs. The Investigator must permit regular study-related monitoring and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based monitoring, as applicable), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

In addition, the Investigator must permit Sponsor-appointed Quality Assurance representatives, the reviewing IRB/REB, or regulatory agency representatives to audit the facilities and documentation at agreed times. An audit is the systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data recorded, analyzed, and accurately reported according to the protocol, Sponsor/designee/CRO's SOPs, GCP and applicable regulatory requirements. Auditors are independent of the clinical trial and its performance.

10.3.3. Protocol Amendments

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/REB and to the appropriate regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/REB and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10.3.4. Protocol Deviations

The Investigator should document and explain any protocol deviations occurring during the study. In addition, the Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/REB in accordance with established IRB/REB policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities.

Prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, will not be allowed.

10.4. Other Operational Considerations

10.4.1. Study and Site Start and Closure

The study start date is the date of the FPFV.

The study end date is the date of the LPLV.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/REB or local health authorities, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator
- Total number of patients enrolled earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the REBs/IRBs, the regulatory authorities, and the CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform all patients still in the study and should assure appropriate patient treatment and/or follow-up.

11. Appendices

11.1. Appendix 1: ACR Criteria for the Diagnosis of Osteoarthritis

Clinical and laboratory	Clinical and radiographic	Clinical ‡
Knee pain	**Knee pain**	**Knee pain**
+ at least 5 of 9:	**+ at least 1 of 3:**	**+ at least 3 of 6:**
- Age > 50 years	- Age > 50 years	- Age > 50 years
- Stiffness < 30 minutes	- Stiffness < 30 minutes	- Stiffness < 30 minutes
- Crepitus	- Crepitus	- Crepitus
- Bony Tenderness	+ Osteophytes	- Bony Tenderness
- Bony enlargement		- Bony enlargement
- No palpable warmth		- No palpable warmth
- ESR <40 mm/hour		
- RF <1:40		
- SF OA		
92% sensitive	*91% sensitive*	*95% sensitive*
75% specific	*86% specific*	*69% specific*

* ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/mm^3).
† Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

Source: Altman et al. 1986

11.2. Appendix 2: Kellgren & Lawrence Grading for Knee Osteoarthritis

The Kellgren & Lawrence system (Kellgren and Lawrence, 1957; Petersson *et al*. 1997) is a method of classifying the severity of knee osteoarthritis according to the following five grades:

Grade	Description
Grade 0	No radiographic features of OA are present
Grade 1	Doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2	Presence of definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3	Multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4	Large osteophytes, marked JSN, severe sclerosis and definitely bony deformity

11.3. Appendix 3: WOMAC for Knee Osteoarthritis (Sample)

WOMAC Survey Form Name: _____

Instructions: In Sections A, B, and C, questions will be asked about your knee pain. Please mark each response with an X. If you are unsure about how to answer a question, please give the best answer you can.

A. Think about the pain you felt in your knee during the last 48 hours.

Question: How much pain do you have?	None	Mild	Moderate	Severe	Extreme
1. Walking on a flat surface	☐	☐	☐	☐	☐
2. Going up and down stairs	☐	☐	☐	☐	☐
3. At night while in bed, pain disturbs your sleep	☐	☐	☐	☐	☐
4. Sitting or lying	☐	☐	☐	☐	☐
5. Standing upright	☐	☐	☐	☐	☐

B. Think about the stiffness (not pain) you have in your knee during the last 48 hours. Stiffness is a sensation of decreased ease in moving your joint.

	None	Mild	Moderate	Severe	Extreme
6. How severe is your stiffness after first awakening in the morning?	☐	☐	☐	☐	☐
7. How severe is your stiffness after sitting, lying, or resting in the day?	☐	☐	☐	☐	☐

C. Think about the difficulty you had in doing the following daily physical activities due to your knee during the last 48 hours. By this we mean your ability to move around and look after yourself.

Question: What degree of difficulty do you have?	None	Mild	Moderate	Severe	Extreme
8. Descending stairs	☐	☐	☐	☐	☐
9. Ascending stairs	☐	☐	☐	☐	☐
10. Rising from sitting	☐	☐	☐	☐	☐
11. Standing	☐	☐	☐	☐	☐
12. Bending to the floor	☐	☐	☐	☐	☐
13. Walking on flat surfaces	☐	☐	☐	☐	☐
14. Getting in and out of a car, or on or off a bus	☐	☐	☐	☐	☐
15. Going shopping	☐	☐	☐	☐	☐
16. Putting on your socks or stockings	☐	☐	☐	☐	☐
17. Rising from the bed	☐	☐	☐	☐	☐
18. Taking off your socks or stockings	☐	☐	☐	☐	☐
19. Lying in bed	☐	☐	☐	☐	☐
20. Getting in or out of the bath	☐	☐	☐	☐	☐
21. Sitting	☐	☐	☐	☐	☐
22. Getting on or off the toilet	☐	☐	☐	☐	☐
23. Performance heavy domestic duties	☐	☐	☐	☐	☐
24. Performing light domestic duties	☐	☐	☐	☐	☐

Source: www.womac.org

11.4. Appendix 4: Skin Irritation Scale

Skin irritation will be assessed using the Berger/Bowman Scoring Scale (Berger and Bowman, 1982; US FDA Guidance 2018b), comprised of the Dermal Response (Table 8) and Other Effects (Table 9) scoring system:

Table 8 Dermal Response Scoring System

Skin Appearance	Score
No evidence of irritation	**0**
Minimal erythema that is barely perceptible	**1**
Definite erythema that is readily visible and minimal edema or minimal papular response	**2**
Erythema and papules	**3**
Definite edema	**4**
Erythema, edema, and papules	**5**
Vesicular eruption	**6**
Strong reaction spreading beyond the application site	**7**

Table 9 Other Effects Scoring System

Score (Numeric Equivalent)	Observation
A (0)	Slightly glazed appearance
B (1)	Marked glazed appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the application site
H (3)	Small petechial erosions and/or scabs

When an *Other Effects* score is observed, the score should be reported as both a:

- Number and letter combination score; and
- Numerical total (Dermal Response score + Other Effects numerical score).

Table 10 lists some examples of the combination score and numerical total scores to be reported.

Table 10 Reporting Skin Irritation Scores

Dermal Response Score	Other Effects Score*	Combination Score[1]	Numerical Total[2]
0	–	0 –	0
1	C (2)	1 C	3
4	–	4 –	4
7	G (3)	7 G	10
2	A (0)	2 A	2

[1] Combination Score is expressed as the 'Dermal Response' numerical score followed by the 'Other Effects' letter score.

[2] Total numeric is the sum of the 'Dermal Response' and the numeric equivalent of the 'Other Effects'

* A dash ('-') means 'no other effects' or 'not applicable'.

11.5. Appendix 5: Clinical Laboratory Tests

The tests detailed in Table 11 will be performed by the central laboratory (Dynacare).

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 11 Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	RBC Count Hemoglobin Hematocrit Platelet Count	RBC Indices: MCV MCH MCHC	WBC count with Differential: Neutrophils, Lymphocytes Monocytes, Eosinophils, Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST/SGOT	total cholesterol
	Creatinine [2]	Sodium	ALT/SGPT	HDL-C
	Total Protein	Calcium	ALP	LDL-C
	Albumin	Magnesium	Total bilirubin	Triglycerides
	LDH	Glucose (nonfasting)	GGT	
Coagulation	aPTT, INR, Prothrombin Time			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrites, leukocytes by dipstick • Microscopic examination (if the urine blood, protein, or leukocyte test is abnormal)			
Pregnancy testing	Highly sensitive urine hCG pregnancy test (for women of childbearing potential) [3].			
Screening only	Serology: HIV antibody, HBsAg, and HCV antibody			

[1] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 [Liver Chemistry Stopping Criteria]. As a standard precautionary measure, all events of ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and INR >1.5, which may indicate severe liver injury (possible Hy's Law), must be reported to Medical Monitor in an expedited manner.

[2] Serum creatinine-based estimation of eGFR will be completed as described in Appendix 7.

[3] Local urine testing will be used unless serum testing is required by local regulation or IRB/REB. If a urine pregnancy test is positive, it must be confirmed by a serum hCG pregnancy test.

Abbreviations: ALP=alkaline phosphatase ALT=alanine aminotransferase; apTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=Estimated Glomerular Filtration Rate; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; HIV=human immunodeficiency virus; INR=(prothrombin) International Normalized Ratio; LDH=lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol; MCH=Mean Corpuscular Hemoglobin; MCHC=Mean Corpuscular Hemoglobin Concentration; MCV=Mean Corpuscular Volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

Investigators must document their review of each laboratory safety report.

11.6. Appendix 6: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.6.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.6.2. Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical

intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

11.6.3. Recording of AEs and SAEs and Reporting Period

AE Recording

- Investigators (or qualified designees) will seek information on AEs at each patient contact. All AEs occurring between the Screening Visit and the Week 6/EOS Visit, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. After the Week 6/EOS Visit, AE recording (and reporting as applicable) will be limited to the following: updates to AEs that were ongoing at the time of the Week 6/EOS Visit, new onset AEs that are assessed by the Investigator as possibly, probably, or certainly related to the study drug, or as an SAE.
- For each AE recorded on the Adverse Event eCRF, the Investigator will provide an assessment of seriousness (see Section 11.6.2 for seriousness criteria), severity (see Section 11.6.4), and causality (see Section 11.6.5).
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE (or SAE).
- Actions in terms of concomitant therapy given to treat the AE will be documented according to the following categories:
  - None
  - Non-drug therapy
  - Drug therapy
  - Drug therapy and non-drug therapy
  - Not available
- Actions taken toward the IMP as a result of the AE will be documented according to the following categories:
  - None
  - Dose(s) skipped
  - Dosing interrupted
  - Drug withdrawn
  - Not applicable (e.g., for pre-treatment AEs/Baseline complaints)

- Unknown (this designation may only be used if the patient is lost to follow-up or withdrew consent from all further study participation and contacts.)

SAE Recording

- When an SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports, as applicable) related to the event.
- The Investigator will then record all relevant SAE information on the SAE Report Form and the Adverse Event eCRF.
- For each SAE, the Investigator will provide an assessment of seriousness (see Section 11.6.2 for seriousness criteria), severity (see Section 11.6.4), and causality (see Section 11.6.5). However, completion of these assessments should not delay reporting of the SAE to the Pharmacovigilance (PV) and Safety Manager (see Section 11.6.6).
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the PV and Safety Manager in lieu of completion of the SAE Form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor, Medical Monitor, or PV and Safety Manager. In this case, all patient identifiers, with the exception of the study-specific patient ID number and key demographic data (as permitted by the local IRB/REB policies), will be redacted on the copies of the medical records before submission to the PV and Safety Manager.

11.6.4. Assessment of AE/SAE Intensity

Assessment of Intensity

The Investigator will provide an assessment of intensity for each clinical and laboratory AE and SAE reported during the study according to the following categories:

- Mild: An event that is either asymptomatic or associated with mild symptoms that are easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities, and not requiring intervention.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday age-appropriate activities and/or requires minimal, local, or non-invasive intervention.
- Severe: An event that prevents normal everyday activities, and requires intervention (such as pharmacological treatment, surgical intervention, hospitalization, etc.)

  Note: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Section 11.6.2), NOT when it is rated as severe.

11.6.5. Assessment of AE/SAE Causality

Assessment of Causality

- The Investigator is required to assess the relationship between the study drug and each occurrence of each AE/SAE according to the following categories:
  - **Not related**: Sufficient evidence exists to conclude that there is no causal relationship to study drug administration (i.e., no temporal relationship to study drug administration or proved other cause).
  - **Unlikely related**: Sufficient evidence to exclude a causal relationship is lacking; however, there is also no evidence or argument to suggest a causal relationship to study drug administration (e.g., a temporal relationship to study drug administration which makes a causal relationship improbable, and other drugs, chemicals or underlying disease[s] provide plausible explanations).
  - **Possibly related**: Limited evidence or argument exists to suggest a causal relationship (e.g., a reasonable time sequence to administration of the study drug but could also be explained by concurrent disease(s) or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear).
  - **Probably related**: Sufficient evidence or argument exists to suggest a causal relationship (e.g., a reasonable time sequence to administration of the study drug, unlikely to be attributed to concurrent disease(s) or other drugs or chemicals. Clinically reasonable response on withdrawal [dechallenge].)
  - **Certainly related**: Clear evidence exists for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study drug administration, which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [dechallenge] should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure, if necessary).
- Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE/SAE is considered to be related to study drug. The following guidance should be taken into consideration when determining the causality of an AE/SAE:
  - Temporal relationship of the event onset to the study drug administration;
  - Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors;
  - Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
  - Known association of the event with the disease under study
  - Known association of the event with the study drug or with similar treatments

- For each AE/SAE, clinic/medical notes must indicate that the Investigator has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which the Investigator has minimal information for a reliable assessment of causality to be included on the Initial SAE Report Form. Completion of the causality assessments should not delay the initial reporting of the SAE to the PV and Safety Manager (see Section 11.6.6). However, the Investigator's assessment of causality must be submitted as soon as possible (no later within 24 hours) on a Follow-up SAE Report From.
- The Investigator may also change his/her causality assessment in light of follow-up information obtained and send an SAE Follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining requirements for expedited regulatory reporting of the SAE.

11.6.6. Reporting of SAEs

SAE Reporting via an Electronic SAE Data Collection Tool

- The primary mechanism for reporting an SAE to the PV and Safety Manager will be the electronic SAE data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE Report Form (see next section) to report the event within 24 hours of learning about the event.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic SAE data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the PV and Safety Manager by telephone, followed by the submission of a duly completed and signed SAE Report Form (no later than within 24 hours of the telephone notification).
- Contacts for SAE reporting are as follows:
  - PV and Safety Manager
  - Email: pharmacovigilance@veristat.com
  - Telephone: 1-888-662-0657
  - Fax: 1-888-662-0647

SAE Reporting via Paper SAE Report Form

- Facsimile or e-mail transmission of the SAE Report Form is the preferred method to transmit this information to the PV and Safety Manager.

- In rare circumstances, notification by telephone is acceptable, followed immediately after (within 24 hours of the telephone notification) by the submission of a duly completed and signed SAE Report Form.
- Contacts for SAE reporting are as follows:
  - PV and Safety Manager
  - Email: pharmacovigilance@veristat.com
  - Telephone: 1-888-662-0657
  - Fax: 1-888-662-0647

11.6.7. AE and SAE Follow-up and Outcomes

Follow-up of AEs and SAEs

- The Investigator should follow each AE/SAE until the event has resolved to Baseline level or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent.
- Every effort should be made to follow all SAEs considered to be related to the study drug until a final outcome can be reported. Follow-up in case of SAEs may include arrangements for the conduct of supplemental measurements and/or evaluations (e.g., additional laboratory tests or investigations, or consultation with other health care professionals) as medically indicated or as requested by Medical Monitor (to elucidate the nature and/or causality of the event as fully as possible). The Investigator is required to submit any updated SAE data to the PV and Safety Manager within 24 hours of receipt of the follow-up information.
- For each AE, the event outcome (with date) should be documented on the Adverse Event eCRF and in the patient's medical record (and on the Final SAE Report Form for each SAE), using one of the following categories:
  - Resolved
  - Resolved with sequelae
  - Resolving
  - Not resolved/Ongoing
  - Fatal
  - Unknown (this designation may only be used if the patient is lost to follow-up or withdrew consent from all further study participation and contacts.)

11.7. Appendix 7: Estimated Glomerular Filtration Rate

Estimated Glomerular Filtration Rate (GFR) will be calculated either by the central laboratory, or manually, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al. 2009; Levey et al. 2010):

- For females:

$$eGFR = 141 \times \min(SCr/0.7, 1)^{-0.329} \times \max(SCr/0.7, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \times 1.159 \text{ [if Black]}$$

- For males:

$$eGFR = 141 \times \min(SCr/0.9, 1)^{-0.411} \times \max(SCr/0.9, 1)^{-1.209} \times 0.993^{Age} \times 1.159 \text{ [if Black]}$$

where

- eGFR is expressed in mL/min/1.73 m^2
- SCr is serum creatinine in mg/dL
- min is the minimum of SCr/0.7 or 1 (for females) or the minimum of SCr/0.9 or 1 (for males)
- max is the maximum of SCr/0.7 or 1 (for females) or the maximum of SCr/0.9 or 1 (for males)
- Age is expressed in years.

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