# CLINICAL STUDY PROTOCOL

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| Title: | AN INTERNATIONAL, MULTICENTRE, DOUBLE-BLIND, RANDOMISED STUDY OF THE EFFECT OF DIACEREIN VS CELECOXIB ON SYMPTOMS AND STRUCTURAL CHANGES IN SYMPTOMATIC KNEE OSTEOARTHRITIS PATIENTS AS ASSESSED BY MAGNETIC RESONANCE IMAGING |
| Protocol number | DAR-INT-14-01 |
| EudraCT number | 2015-002933-23 |
| Investigational Product | Diacerein |
| Sponsor | TRB CHEMEDICA INTERNATIONAL SA<br>Rue Michel Servet 12<br>Case postale 352<br>Geneva 12 Switzerland CH-1211<br>Phone: 41 22 703 4911<br>Fax: 41 22 703 4901 |
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| Version Number | 2.2 |
| Date | March 22, 2019 |
| Confidentiality | This document contains information that should be kept confidential to those responsible for the execution and organisation of this protocol. It is intended only for the use of such persons, and should |

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| | not be disseminated except with the express permission of the Sponsor. |
| Ethic statement | The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki. |

## SIGNATURE PAGE

## COMMITMENT

- I agree to take part in the study entitled: An international, multicentre, double-blind, randomised study of the effect of Diacerein vs. Celecoxib on symptoms and structural changes in symptomatic knee osteoarthritis patients as assessed by magnetic resonance imaging (Protocol number: DAR-INT-14-01, version 2.2)
- EudraCT #: 2015-002933-23
- I have read the protocol and I accept the conditions.
- I fully agree to take part in this study in accordance with the Declaration of Helsinki (see Appendix I) and with the Good Clinical Practice guidelines.

**Lead Principal Investigator**

Signature | Date (dd/mm/yy)

Jean-Pierre Raynauld, MD, FRCPC

**ARTHROLAB INC**

Signature | Date(dd/mm/yy)

Jean-Pierre Pelletier, MD, FRCPC, CEO

**SPONSOR**

**TRB CHEMEDICA INTERNATIONAL SA**

Signature | Date (dd/mm/yy)

Alessandro Di Napoli, Pharm.D. Vice-President, Marketing and Scientific

**Biostatistician**

Signature | Date (dd/mm/yy)

Sylvie di Nicola
Inferential

## PROTOCOL AGREEMENT

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements, ICH guidelines, and the declaration of Helsinki.

**INVESTIGATOR:**

Investigator Signature: _____

Date: (dd/mm/yy) _____

Investigator Name and Title: _____

Study Site Number: _____

Address and Telephone Number: _____

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**PROTOCOL SYNOPSIS**

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| **Study Title** | An international, multicentre, double-blind, randomised, study of the effect of Diacerein vs. Celecoxib on symptoms and structural changes in symptomatic knee osteoarthritis patients as assessed by magnetic resonance imaging |
| **Internal ref. no. (or short title)** | DAR-INT-14-01. |
| **Clinical Phase** | Phase III/IV |
| **Study Centres** | Approximately 11 centres in Quebec and Ontario, Canada and approximately 17 centres in Europe (Spain, Austria, Czech Republic and Belgium). |
| **Investigators** | Lead principal investigator: Jean-Pierre Raynauld (Montreal, Canada). |
| **Study Design** | International, multicentre, double-blind, randomised, two-parallel groups study. |
| **Study Participants** | Men and women of at least 50 years of age, with primary and symptomatic knee osteoarthritis (OA) complying with the classification criteria of OA of the knee established by the American College of Rheumatology (ACR), whose condition could benefit from symptomatic treatment with Diacerein. |
| **Planned Sample Size** | 400 patients (200 patients for each treatment arm) are deemed sufficient to permit an evaluation of Diacerein efficacy on disease symptoms (pain). |
| **Treatment duration** | 182 days (symptom study) and 728 days (MRI structural study). |
| **Planned Study Period** | Study may last up to 3 years, including recruitment and treatment. |

**Key Inclusion/Exclusion Criteria**
For all inclusion/exclusion criteria see Section 8.1 and 8.2.

**Key Inclusion criteria:**

1. Patients with OA of radiological stages 2 and 3 according to Kellgren-Lawrence.
2. Patients with a minimum joint space width ≥ 2 mm in the medial tibiofemoral compartment on standing knee X-ray **(MRI structural study only).**
3. Patients with knee pain on most days of the month before entering into the study
4. Patients with a visual analogue scale (VAS) pain score (0-100 mm) while walking on a flat surface ≥ 40 mm at Screening (Visit 1) and Inclusion (Visit 2) visits.

**Key Exclusion criteria:**

5. Patients with other bone and articular diseases (antecedents and/or current signs)
6. Patients with isolated knee lateral compartment OA defined by joint space loss in the lateral compartment only.
7. Patients with Class IV functional capacity using the American Rheumatism Association criteria.
8. Patients who have had surgery in any lower limb or arthroscopy, aspiration or lavage in any lower limb joint within 180 days of the Inclusion Visit (Visit 2).

9. Patients who have had meniscal surgery on the study knee.
10. Patients who have undergone total knee replacement in the contralateral knee within 182 days prior to the Screening Visit (Visit 1).
11. Patients using corticosteroids (oral, injectable; exception of intra-articular/soft tissue injection at the exclusion of the target knee), indomethacin, therapeutic dose of glucosamine or chondroitin sulphate or Diacerein or Avocado-Soybean Unsaponifiables during the 12 weeks preceding inclusion (intra-articular injections of corticosteroids in the contralateral knee is allowed during the study).
12. Patients using hyaluronic acid (intra-articular target knee) during the 26 weeks preceding inclusion.
13. Patients with a known history of diarrhoea, more particularly if 65 and older.
14. Patients who have significant risk factors for heart attack or stroke will be assessed carefully. Risk factors for heart attack and stroke include high blood pressure (treated or untreated), high cholesterol, diabetes and smoking. The global risk assessment will be assessed with the American Heart Association assessment of cardiovascular (CV) risk tables. Patients with high risk of CV events will be excluded.

**Objectives:**

The primary objective of this study is to show that Diacerein is non-inferior to Celecoxib in terms of pain reduction (WOMAC A pain subscale) after 182 days of treatment in symptomatic knee OA patients.

Exploratory objectives:

Exploratory objectives include analyses comparing Diacerein with Celecoxib on other functional parameters and structural changes as assessed by MRI after 24 months (728 days) and safety as follows:

1. Cartilage volume loss, bone marrow lesions, synovitis, meniscal extrusion, using MRI, at 728 days (MRI structural study only).
2. Disease symptoms:
   a) WOMAC pain at 728 days
   b) WOMAC global stiffness and function subscales at 182 and 728 days
   c) Pain according to Huskisson's visual analogue scale (VAS 0 – 100 mm) at 182 and 728 days
   d) OARSI set of responder criteria at 182 and 728 days
   e) Assessment of the presence of joint swelling and/or effusion at 182 and 728 days
   f) Consumption of rescue medication at 182 and 728 days
   g) Patient's global assessment of disease activity at 182 and 728 days
   h) Investigator's global assessment of disease activity at 182 and 728 days
   i) Patient's global assessment of response to therapy at 182 and 728 days
   j) Investigator's global assessment of response to therapy at 182 and 728 days
   k) Health status according to SF-36 at 182 and 728 days
3. Clinical safety of both products after short (182 days) and long-term (728 days) treatment.

| **Investigational Medicinal Product, Dose and Mode of Administration** | |
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| Diacerein: one Diacerein 50 mg capsules once daily with meals (dinner) in the evening for the first month then twice daily with meals in the morning (breakfast) and the evening (dinner). |
| **Reference Therapy, Dose and Mode of Administration** |
| Celecoxib: one Celecoxib 200 mg capsule once daily in the morning (breakfast) and one placebo capsules once daily in the evening (dinner). |
| **Placebo, Dose and Mode of Administration** |
| Placebo: one placebo capsule once daily in the evening (dinner) for patients treated in the Celecoxib group and one placebo capsule once daily in the morning (breakfast) for patients treated in the Diacerein group only during the first month of treatment. |
| **Study assessments**<br>Study assessments will be performed from screening to Visit 5 (D182) for all patients included in the study and from screening to Visit 10 (D728) in a subgroup of patients involved in the MRI structural study.<br><u>Signs and Symptoms</u><br>▪ The WOMAC will be assessed at Inclusion Visit (Visit 2, D0), Visit 3 (D60), Visit 4 (D120), Visit 5 (D182), Visit 7 (D364), Visit 9 (D546), and Visit 10 (D728).<br>▪ Pain will be assessed using a visual analogue scale (VAS) at Screening (Visit 1), Inclusion Visit (Visit 2, D0), Visit 3 (D60), Visit 4 (D120), Visit 5 (D182), Visit 7 (D364), Visit 9 (D546), and Visit 10 (D728).<br>▪ The SF-36 questionnaire will be administered at Inclusion Visit (Visit 2, D0), Visit 3 (D60), Visit 4 (D120), Visit 5 (D182), Visit 7 (D364), Visit 9 (D546), and Visit 10 (D728).<br>▪ Patient's and Investigator's global assessment of disease activity at Inclusion Visit (Visit 2, D0), Visit 3 (D60), Visit 4 (D120), Visit 5 (D182), Visit 7 (D364), Visit 9 (D546), and Visit 10 (D728).<br>▪ Patient's and Investigator's global assessment of response to therapy at Visit 3 (D60), Visit 4 (D120), Visit 5 (D182), Visit 7 (D364), Visit 9 (D546) and Visit 10 (D728).<br><br><u>MRI of the knee assessments by the central laboratory</u><br>MRI will be performed at Inclusion (Visit 2, D0), Visit 7 (D364) and Visit 10 (D728) and centrally reviewed. The following measurements will be performed.<br>▪ Cartilage volume loss in the global knee and in the medial and lateral compartments.<br>▪ Bone marrow lesions (BML) score.<br>▪ Presence or absence of meniscal extrusion.<br>▪ Evaluation of synovitis (synovial membrane thickness).<br><br><u>Safety assessments</u><br>▪ Adverse events at each visit including phone calls at D273 (Visit 6) and D455 (Visit 8).<br>▪ Laboratory tests at Screening (Visit 1), Visit 3 (D60), Visit 4 (D120), Visit 5 (D182), Visit 7 (D364), Visit 9 (D546), and Visit 10 (D728). |

- Clinical examinations and blood pressure at Screening (Visit 1), Visit 5 (D182), Visit 7 (D364), and Visit 10 (D728).

**Study Endpoints**

**Primary efficacy endpoint:**

Change from baseline (Visit 2) in WOMAC Pain subscale after 182 days of treatment.

**Exploratory efficacy endpoints (structural changes by MRI):**

- Cartilage volume loss from baseline (Visit 2) at D728 in the global knee and in the medial and lateral compartments.
- Change from baseline (Visit 2) at D728 in BML score.
- Change from baseline (Visit 2) at D728 of synovitis (synovial membrane thickness).

**Exploratory efficacy endpoints (Signs and symptoms):**

- Change from baseline (Visit 2) in WOMAC Pain score at D728.
- Change from baseline (Visit 2) in WOMAC Stiffness and WOMAC function score at D182 and D728.
- Change from baseline (Visit 2) in using a visual analogue pain scale (VAS - Huskisson's) at D182 and D728.
- Percentage of OARSI (Osteoarthritis Research Society International) responders at D182 and D728.
- Percentage of patients with joint swelling and effusion at D182 and D728.
- Percentage of patients consuming rescue medication at D182 and D728.
- Change from baseline (Visit 2) in Patient's global assessment of disease activity at D182 and D728.
- Change from baseline (Visit 2) in Investigator's global assessment of disease activity at D182 and D728.
- Patient's global assessment of response to therapy at D182 and D728.
- Investigator's global assessment of response to therapy at D182 and D728.
- Change from baseline (Visit 2) in Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from the SF-36 at D182 and D728.

**Statistical Method:**

**Sample size calculation**

The sample size calculation has been established to test the non-inferiority of Diacerein vs. Celecoxib in the assessment of the change from baseline (Visit 2) in WOMAC pain subscale score at 182 days.

Assuming that:

- the mean decrease in WOMAC Pain score at 182 days in the Diacerein treatment group will be the same as in the Celecoxib treatment group,
- a common standard deviation of 26 in the two treatment groups,
- a type I error set to $\alpha = 0.025$ (one-sided condition) and (1-beta) power equal to 90%,
- and using PROC POWER in SAS® Version 9.2, the estimation provided for the one-sided, two sample Student's t-test with equal allocation to two groups, 144 patients per treatment group is deemed to have adequate power to claim non-inferiority with a margin of 10 units. To allow for approximately 25% drop out, 200 patients will be

recruited per treatment group, i.e. 400 patients in total.

**Study Population**

Due to the design of the study – the primary analysis being conducted at 6 months on the 400 included patients in the symptoms part of the study; the 24 months analysis being conducted on approximately 100 patients (from Canada only) participating to the structural study – two sets of Analyses Populations will be defined: one for the analyses at 6 months, including the primary efficacy analysis, and one for the analyses at 24 months.

**Study population for the 6-months analysis (primary efficacy analysis)**

- The Safety (SAF) population will be composed of all patients who took at least one dose of the study medication. Analyses on the SAF will be performed according to the product actually received.

- The Intent-to-Treat (ITT) population will be composed of all randomised patients who received at least one dose of the study medication, had an efficacy measurement at inclusion and at least one corresponding post-inclusion efficacy measurement (for the primary efficacy variable).

  Analyses on the ITT population will be performed according to the randomisation group regardless of the study medication actually received.

- The Per-Protocol (PP) population will be a subset of the ITT population and will include all patients who did not present any major violation of the protocol over the 6-month follow-up period.

**Study population for the analysis at 24 months (Structural study)**

Due to the exploratory nature of the analyses, the population will be composed of all per-protocol population (PP) patients randomized and treated, and being selected for the 24 months structural study will be analysed. Reasons for exclusion from the aforementioned PP population will be further described in the SAP. Analyses of the ITT population will also be performed to test the robustness of the results.

**Analysis of the primary efficacy endpoint**

- The primary efficacy analysis will be based on the PP population and will also be performed using the ITT population to test the robustness of the results.
- Non-inferiority of Diacerein versus Celecoxib will be assessed by computing the difference in the mean change from baseline (Visit 2) in WOMAC Pain subscale score after 182 days of treatment between Diacerein and Celecoxib treatment groups.
- For non-inferiority claim, Diacerein will be proven to be non-inferior to Celecoxib if the upper bound of the 95% CI of the difference in the mean change from baseline at D182 between Diacerein and Celecoxib is inferior to 10 (on a scale of 0-100). A p-value for the non-inferiority testing between the two treatment groups will be obtained using a one-sided Student t-test.

**Analysis of exploratory efficacy endpoints**

- All other efficacy and safety statistical results will be exploratory. No adjustment to control the type I error for multiplicity will be performed. For all other analyses than

primary, statistical tests will be two-sided at 5% significance level. Statistical significance will be declared if the rounded p-value will be less than 5%.

- The difference in mean change from baseline between Diacerein and Celecoxib treatment groups will be tested, for exploratory purposes, with a Student t-test (Gaussian variable) or a Mann-Whitney test (non-Gaussian variable). Likewise, the comparison between Diacerein and Celecoxib treatment groups will be analysed with either a Chi-square or a Fisher exact test for qualitative data.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACR | American College of Rheumatology |
| AE | Adverse Event |
| AHA | American Heart Association |
| ALT | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| ANCOVA | Analysis of Covariance |
| ASA | Acetyl Salicylic Acid |
| AST | Aspartate Aminotransferase |
| ASU | Avocado-Soybean Unsaponifiables |
| ATC | Anatomical Therapeutic Chemical |
| BID | Twice Daily |
| BMI | Body Mass Index |
| BML | Bone Marrow Lesion |
| BUN | Blood Urea Nitrogen |
| ˚C | Degree Celsius |
| CBC | Complete Blood Count |
| Coxib | Cyclooxygenase Inhibitor |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CRP | C-Reactive Protein |
| CV | Cardiovascular |
| D | Day |
| DIE | Daily |
| DMOAD | Disease Modifying Osteoarthritis Drug |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| e-CRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| ESR | Erythrocyte Sedimentation Rate |
| GCP | Good Clinical Practice |
| FSH | Folliculo-Stimulating Hormone |
| GI | Gastro-intestinal |
| GIU | Gastro-intestinal Ulceration |
| H | Hour |
| HDL | High Density Lipoprotein |
| HIV | Human Immunodeficiency Virus |
| IEC | Independent Ethic Committee |
| ICH | International Conference on Harmonisation |
| IL-1 | Interleukin-1 |
| IRB | Institutional Review Board |
| ITT | Intent-To-Treat |
| JSN | Joint Space Narrowing |
| JSW | Joint Space Width |
| LDL | Low Density Lipoprotein |
| MCS | Mental Component Summary |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MAR | Missing at Random |
| mg | Milligram |
| mm | Millimetre |

| | |
|---|---|
| MMP | Matrix Metalloproteinase |
| MRI | Magnetic Resonance Imaging |
| N | Number |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| NYHA | New York Heart Association |
| OA | Osteoarthritis |
| OARSI | Osteoarthritis Research Society International |
| PCS | Physical Component Summary |
| $PGE_2$ | Prostaglandin $E_2$ |
| PP | Per-Protocol |
| PPI | Proton Pump Inhibitor |
| RBC | Red Blood Cells |
| ROI | Region of Interest |
| SAE | Serious Adverse Event |
| SAF | Safety Population |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse Reaction |
| SERM | Selective Estrogen Receptor Modulator |
| SF-36 | Short Form-36 |
| SmPC | Summary of Product Characteristics |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| SR | Sedimentation Rate |
| SySADOA | Symptomatic Slow-Acting Drug for OA |
| TSH | Thyroid-Stimulating Hormone |
| TNF-α | Tumour Necrosis Factor-α |
| UGI | Upper Gastrointestinal Tract |
| ULN | Upper Limit of Normal |
| V | Visit |
| VAS | Visual Analogue Scale |
| WBC | White Blood Cells |
| WHO | World Health Organization |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

# 1 GENERAL INFORMATION

## 1.1 Sponsor

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## 1.2 Lead Principal Investigator

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## 1.3 Investigation Centres

Approximately 11 investigative sites in Canada and approximately 17 sites in Europe (Spain, Austria, Czech Republic, and Belgium) will be invited to take part in this international study.

## 1.4 Medical Monitor and Medical Expert

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### 1.5 Contract Research Organisations

| CRO | Responsibilities | Address |
|---|---|---|
| ARTHROLAB INC | Project Management / Central review of MRI | 1871 Sherbrooke Street East, Montreal, Quebec, Canada. |
| MEDQUALIS INC | Contract Research Organisation (CRO) Monitoring in Canadian clinical centres | 1240 Beaumont Ave, Suite 208, Mont-Royal, Quebec, Canada |
| KEYRUS BIOPHARMA | CRO, Monitoring in European clinical centres | 18/20 rue Clément Bayard – 92300 Levallois-Perret Cedex –France |
| | | |
| ROPACK INC | Randomisation, packaging, labelling | 10801 Mirabeau, Montréal, Québec H1J 1T7 Canada |
| INFERENTIAL/ EURAXI PHARMA | Data management Biostatistics and Medical writing | 35 rue Godot de Mauroy, 75009 Paris, France. |
| CSM Europe SA | Packaging and labelling (backup) European Storage and Distribution; European QP release | Watson & Crick Hill<br>Rue Granbonpré 11<br>B-1435 Mont-Saint-Guibert<br>Belgium |
| PharmaLex GmbH | Pharmacovigilance | Bahnstr.42-46<br>D-61381 Friedrichsdorf<br>Germany |

### 1.6 Study Committee

**Data Safety Monitoring Board (DSMB)**

An independent Data and Safety Monitoring Board (DSMB) will be established prior to study enrolment. All members will be independent from the Sponsor and the participating investigators. The DSMB will periodically monitor patient safety information and review the progress of the clinical study. The DSMB will make recommendations regarding the continuation, suspension or termination of this clinical study.

# 2 BACKGROUND INFORMATION

## 2.1 Osteoarthritis of the Knee

Osteoarthritis (OA) of the knee is the most frequent cause of knee pain after the age of 50 years. It is also the most frequent form of OA (3 times more frequent than hip OA). Knee OA results in part from mechanical problems and the principal intervening risk factors include genetics, obesity and traumatic factors (meniscal lesion, rupture of the anterior cruciate ligament, articular fracture and others).

The onset is often progressive and knee OA progresses more often in the first phase in an intermittent mode with painful outbreaks interrupted by symptom-free intervals, followed by continuous symptomatology. The main symptoms are pain and functional disability.

In the event of synovitis, one can observe an increase in pain, articular stiffness, and articular effusion with inflammatory signs including slight local warmth of the joint.

## 2.2 Pathophysiology of OA

OA is a joint disease characterised by articular cartilage loss associated with structural changes in the cartilage, subchondral bone, and synovial membrane as well as the periarticular structures.

OA leads to molecular, biochemical, cellular, biomechanical and major morphological modifications of the articulation, leading progressively to articular cartilage loss, subchondral bone lesions, cyst formations and osteophyte formation.

In OA, the cartilage matrix degradation is primarily due to enzymes, in particular the matrix metalloproteinases (MMPs), themselves controlled by cytokines and chemokines. At least two cytokines play a major role in OA, interleukin 1 (IL-1) and tumour necrosis factor-α (TNF-$\alpha$) [1].

The breakdown products of the cartilage released in the synovial fluid will be phagocytosed by the synovial membrane which will respond with an ensuing inflammatory reaction. The inflammation of the synovial membrane in OA causes the macrophages, synoviocytes and fibroblasts to produce free radicals, prostaglandin $E_2$ ($PGE_2$), IL-1, and MMPs, which in turn contribute to cartilage destruction.

## 2.3 OA Treatment

The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatments. In addition to the general measures (weight reduction, patient education, knee care advice, regular exercise, use of assistive devices), pharmacological intervention is often required to alleviate pain, stiffness and inflammation.

The most commonly used medicinal therapies for symptomatic treatment of OA are fast-acting analgesics and/or anti-inflammatories [2]. Long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with well described cardiovascular (CV), gastrointestinal, hepatic, renal and other adverse drug reactions and with drug-drug interaction problems. Symptomatic slow acting drugs for OA (SySADOAs) have symptomatic effects without the safety concerns associated with long term use of NSAIDs and may also modify joint structure. SySADOAs are also characterised by a slow onset of action and a global efficacy at reducing OA symptoms comparable to that of NSAIDs, but they also possess an additional

beneficial effect, called the carry-over effect. This means that the positive effect of the treatment could last for weeks or months following treatment interruption.

### 2.4 Description of the Studied Product: Diacerein

Diacerein, an anthraquinone derivative, has been shown to inhibit the production and activity of the cytokine IL-1β in *in vitro* and *in vivo* studies [3, 4]. This will prevent the IL-1β effect of reducing production of cartilage-specific macromolecules. Diacerein has also been shown to down-regulate IL-1β stimulated secretion of MMPs and aggrecanases, and thereby prevent breakdown of cartilage by these enzymes [5]. A further potential advantage of using Diacerein in OA treatment is that Diacerein does not affect the synthesis of prostaglandins [6] and therefore does not have a deleterious effect on the upper gastrointestinal tract [7]. This is an important advantage compared to NSAID treatment. In addition, Diacerein did not show any CV toxicity when high doses (which were several times the recommended human daily dose) were administered, orally, daily to live dogs [8].

Diacerein has been granted a marketing authorisation in Czech Republic in 2000 and in Austria and Spain in 2002 and is indicated for “specific long-term oral treatment of degenerative joint disease (osteoarthritis and related diseases)”.

### 2.5 Summary of the Benefits and Known Potential Risks of Diacerein and Celecoxib in the Treatment of OA

OA is one of the most common joint disorders. The goals of OA therapy aim at decreasing pain and maintaining or improving joint function. Analgesics, NSAIDs, and cyclooxygenase inhibitor (coxibs) are widely used for symptomatic pain relief. However, long-term use of these drugs can induce a number of potentially serious side effects, particularly in the elderly. For this reason, attention has recently been focused on the investigation and development of new types of drugs and treatments that can improve the clinical symptoms of OA and show better safety profiles, such as SySADOAs [9].

There is evidence that Diacerein has both a symptomatic and a structural effect on cartilage, and clinical studies suggest that Diacerein therapy significantly decreases OA symptoms when compared to placebo [10, 11]. A recent Cochrane review, evaluating the efficacy and safety of Diacerein in the treatment of knee and/or hip OA, concludes that Diacerein treatment has a small, but persistent improvement in pain [12] with the potential benefit of a lack of gastrointestinal toxicity. The most frequent adverse events associated with Diacerein 100 mg daily reported to date were soft stools and diarrhoea, which were reported in about 30% of the patients. These events were generally mild to moderate and, in general, disappeared with continuing treatment. Elevated serum liver enzymes and cases of symptomatic acute hepatic injury have been reported in the post-marketing phase with Diacerein. In clinical studies, around 0.5% of patients on Diacerein had some kind of liver reaction, with most cases being mild, reversible increases in serum transaminases. The proportion of patients who develop drug-induced liver injury following treatment with Diacerein is estimated to be 0.03% [13].

In September 2014, the European Medicines Agency (EMA) recommended to restrict the use of Diacerein-containing medicines in order to manage the risks of severe diarrhoea and effects on the liver "in patients aged 65 years and above. It is also advised that patients start treatment with half the normal dose (i.e., 50 mg daily) for the first month of treatment and should stop Diacerein if diarrhoea occurs. Diacerein should not be used in patients with liver disease or a history of liver disease, and doctors should be monitoring their patients for early signs of liver problems” [14].

Celecoxib is recognised as the current gold standard in the treatment of knee OA. The clinical effectiveness of Celecoxib in the treatment of OA of the knee and hip was demonstrated in several placebo- and active-controlled clinical studies. Celecoxib demonstrated significant reductions in joint pain and disease activity, and also improvement in patient functional activity and health-related quality of life compared to placebo [15]. In OA patients, treatment with Celecoxib 100 mg twice a day or 200 mg once daily resulted in improvement in functional activity as demonstrated by an improvement in pain, stiffness, function and total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

### 2.6 Imaging of OA in DMOAD Studies

Standardised radiographic protocols may provide a valid, reliable and easily reproducible technique for measuring change in joint space width (JSW) over time using serial radiographs. However, in a disease-modifying OA drug (DMOAD) clinical study, based on an estimated rate of joint space narrowing (JSN) of at most 0.15 mm per year, a sample of 2,000 patients would have to be followed for a minimum of two years to reach statistical significance. A study of that magnitude would be costly.

Arthroscopy can also be used to evaluate disease progression as it permits direct visualisation of the cartilage. While this method does appear reliable and sensitive to change at one year [16], it allows assessment of only the cartilage surface and it is only semi-quantitative (i.e., a videotape is sent to an independent, trained evaluator). Most importantly, the technique is invasive. Consequently, large studies requiring repeated assessments are difficult to conduct.

The quality of images obtained using magnetic resonance imaging (MRI) scans makes visualisation of joint structure such as cartilage, bone, and synovium easy. Use of MRI technology to evaluate progression of OA has been limited by the relatively few validated methods by which to quantify the changes observed. The software tool that will be used in this protocol was designed to facilitate the quantification of the status of knee cartilage, by using a modelling technique and analysing images in a precise and reliable way [17-21].

There are advantages of using MRI over serial standardised radiographs in DMOAD studies. First, MR images permit evaluation of all joint structures, including the cartilage, subchondral bone, menisci, synovial tissue and the ligaments. Second, the technology is readily implementable in investigational centres as it relies on conventional MR images. It is now a technology that is fully validated for use in DMOAD studies [20].

### 2.7 Rationale

Given the recent EMA recommendations on Diacerein in patients with osteoarthritis, we propose to determine the efficacy of the product on symptoms and joint structural changes and safety of Diacerein versus Celecoxib, the recognised standard treatment, in a phase III-IV international, multicentre, double-blind, randomised, controlled study.

It is considered that the demonstration of non-inferiority against a recognised standard treatment, after six months of treatment in this population, in addition to meeting ICH International regulations and EMA regulatory guidelines is sufficient and clear evidence of efficacy.

Structural changes will be explored using MRI after a treatment duration of 24 months. This study will provide new efficacy and safety data regarding Diacerein in the treatment of symptomatic knee osteoarthritis.

Choice of Dose of Diacerein and Celecoxib

Patients will receive either Diacerein 100 mg (50 mg twice a day - one 50 mg capsule of Diacerein will be taken with the evening meal for the first month of treatment and then the dose will be 100 mg/day (one 50 mg capsule in the morning and the second capsule in the evening always with meals)) or Celecoxib 200 mg, in the morning with meals, during the treatment period. The dosage regimen and route of administration for both treatment arms have been approved by regulatory agencies and set out in the recommendations for the treatment of OA [12, 15].

Choice of the study Population

The population observed in this study includes men and women of at least 50 years of age, with primary and symptomatic knee OA complying with the classification criteria of OA of the knee established by the American College of Rheumatology (ACR) [22], whose condition could benefit from symptomatic treatment with Diacerein. In addition, patients with a known history of diarrhoea, more particularly if 65 and older, will not be included. In addition, the global risk assessment will be assessed using the American Heart Association (AHA) assessment of CV risk tables (see Appendix VII A) [23]. Patients with high risk of CV events (see Appendix VII B) will be excluded.

# 3 TRIAL OBJECTIVES AND PURPOSE

## 3.1 Purpose of the Study

The purpose of this phase III-IV international, multicentre, double-blind, non-inferiority, randomised, controlled study is to determine the efficacy and safety of Diacerein vs. Celecoxib on symptoms after 6 months of treatment, and on structural changes after 2 years of treatment in knee OA patients as assessed by MRI.

## 3.2 Primary Objective

The primary objective of this study is to show that Diacerein is non-inferior to Celecoxib in terms of pain reduction (using the WOMAC A pain subscale) after 182 days of treatment in symptomatic knee OA patients.

## 3.3 Exploratory Objectives

Exploratory objectives include analyses comparing Diacerein with Celecoxib on other functional parameters and structural changes as assessed by MRI after 24 months (728 days) and safety as follows:

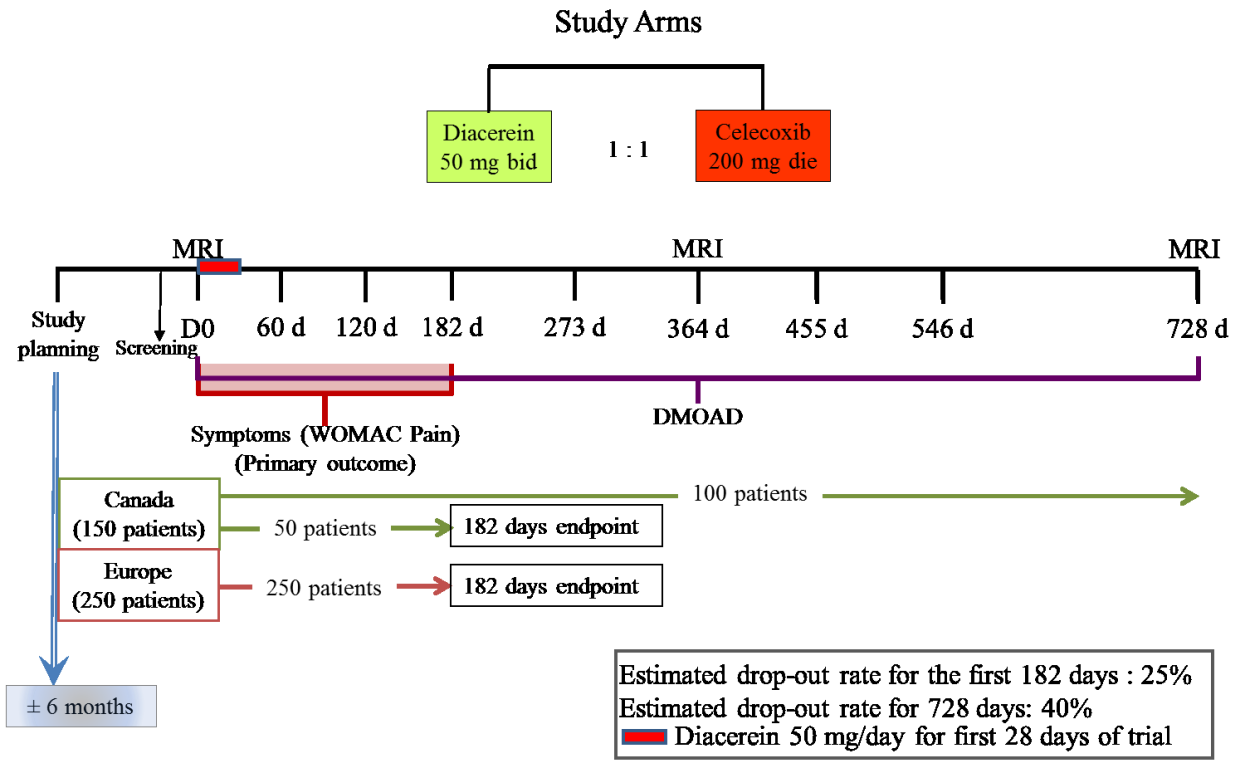
1. Cartilage volume loss, bone marrow lesions, synovitis, meniscal extrusion, using MRI, at 728 days (MRI structural study only).
2. Disease symptoms:
   a. WOMAC pain at D728
   b. WOMAC global stiffness and function subscales at D182 and D728
   c. Pain according to Huskisson's Visual Analogue Scale (VAS 0 – 100 mm) at D182 and D728
   d. Osteoarthritis Research Society International (OARSI) set of responder criteria at D182 and D728
   e. Assessment of the presence of joint swelling and/or effusion at D182 and D728

f. Consumption of rescue medication at D182 and D728
g. Patient's global assessment of disease activity at D182 and D728
h. Investigator's global assessment of disease activity at D182 and D728
i. Patient's global assessment of response to therapy at D182 and D728
j. Investigator's global assessment of response to therapy at D182 and D728
k. Health status according to Short Form 36 (SF-36) at D182 and D728

3. Clinical safety of both products after short (182 days) and long-term (728 days) treatment.

## 4. TRIAL DESIGN

### 4.1 Overall Design




The present study is a phase III (Canada, Belgium) or IV (Spain, Austria, Czech Republic) international, multicentre, double-blind, randomised, controlled, parallel-groups, symptom-modifying and structure-modifying clinical study of Diacerein (50 mg twice daily) versus Celecoxib (200 mg once daily).

It is planned that 400 patients (males and females) of at least 50 years of age will take part in this study (approximately 150 patients in Canada and 250 patients in European countries). All patients will be included after a screening Visit (washout of previous medication for osteoarthritis) and randomised at the inclusion Visit (D0) in 2 treatment groups of 200 patients as follows:

1. **Diacerein arm**: one 50 mg capsule taken once a day for one month and 50 mg twice daily thereafter (n = 200patients).

2. **Celecoxib arm:** one 200 mg capsule once daily (n = 200 patients)

The study has been designed, for its main outcome (WOMAC Pain Subscale at D182) as a non-inferiority clinical study. An additional placebo group was not considered necessary as both treatment groups have already demonstrated superiority over placebo in former randomised controlled studies [10, 12, 14].

Pain and other functional symptoms will be primary analysed after 6 months (182 days) of treatment (symptom study) and MRI structural changes in a subset of randomised patients in selected clinical centres after 24 months (728 days) of treatment (MRI-structural study).

All patients will be assessed at Screening Visit (Visit 1), Inclusion (Visit 2, D0), Visit 3 (D60), Visit 4 (D120), and Visit 5 (D182) (Symptom study).

After Visit 5 (D182), 100 preselected patients from investigational sites in Canada will continue for an additional 18 months double-blind treatment period to explore the DMOAD effect of Diacerein assessed by MRI at D364 and D728. They will be assessed at Visit 6 (Phone call, D273), Visit 7 (D364), Visit 8 (Phone call, D455), Visit 9 (D546), and Visit 10 (D728).

Thus, the duration of the double-blind study will be 182 ± 7 days for the symptom study and 728 ± 15 days from inclusion for the MRI structural study.

During the study, patients will be allowed to take acetaminophen 500 mg, to a maximum of 2 g per day, dispensed at each Visit by the investigator for rescue therapy.

### 4.2 Study Setting

Patients will be enrolled in Canada (approximately 11 centres in the provinces of Quebec and Ontario) and in European countries (approximately 17 centers in Spain, Austria, and Czech Republic and Belgium) in hospitals or clinics. It is expected that each centres will include about 20-30 patients.

### 4.3 Study Conduct

The total duration of the study is expected to be approximately 33-36 months, after the Protocol has been approved by the regulatory authorities and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and the initiation of the centres.

### 4.4 Measures to Minimise/Avoid Bias

The study has been designed as randomised and double-blind to allow unbiased study assessments.

The same investigator is responsible as far as possible for the assessment of all patients in an institution throughout the study so that inter-observer and inter-individual variations are avoided.

<u>Randomisation</u>

A unique randomisation number will be assigned to eligible patients at the end of baseline assessments.

The randomisation table will be generated using a validated computer-program. Treatment allocation depends only on the time sequence in which patients enter the study, thus minimising the selection bias. The study treatments will be allocated by randomisation using a balanced central randomisation. The randomisation list, all the procedures to keep the blind conditions as

well as the packaging and labelling procedures will be conducted by Ropack Inc., Montreal, Quebec, Canada for Canadian part of the study and by CSM Europe SA, Belgium, for the European part.

However, in order to ensure that the investigator has the possibility to access the randomisation code of a patient in case of emergency, two sets of sealed envelopes will be produced. Each envelope will contain the patient number and the treatment allocated. One set of sealed envelopes will be handed over to the investigator at each study centre at the start of the study and the other will be kept by PharmaLex GmbH, the sponsor's pharmacovigilance third party service provider. The investigator will open a sealed envelope only in case of emergency. The reason, date and signature must be written on the opened envelope.

Blinding

The following methods will be used to protect the blinding for both the patients and the investigators:

- Identical outer appearance of Diacerein, Celecoxib, and placebo capsules.
- Identical blisters and cardboard boxes carrying a label that will not disclose the identity of the contents
- Study medication blinded for both investigators and patients during the treatment period.

Patients in both groups will take the same number of capsules daily. Patients in the Diacerein group will take one capsule of Diacerein and one capsule of matched placebo for one month and then two capsules of Diacerein. Patients in the Celecoxib group will take one capsule of Celecoxib and one capsule of a matched placebo.

Celecoxib will be over-encapsulated to match the appearance of Diacerein and placebo.

All analyses regarding the primary outcome measure (non-inferiority of Diacerein compared to Celecoxib in terms of WOMAC pain reduction at D182), other outcome measure and patients' characteristics will be performed once all patients will have completed the 6 month follow-up visit. The double-blind status will be maintained for all other parties (patients, investigator, site personnel) until completion of the study at D728.

None of the supervisory Committees will have access to the code list of treatments allocated to patients, except the authorised persons of the DSMB, who will be responsible for supervising all safety aspects of the study. The unblinded documentation will remain confidential and will not be made available to anyone outside the DSMB up to the end of the 6-months (D182) study part.

### 4.5 Study Endpoints

Due to the design of the study, two sets of statistical analyses will be performed: one after the completion of the 6 months treatment phase of the study in the 400 enrolled patients and another analysis after the completion of 24 months treatment phase in the 100 preselected patients from investigational centres in Canada.

### 4.5.1 Primary Study Endpoint

- Change from baseline (Visit 2, D0) in WOMAC Pain subscale after 182 days of treatment.

### 4.5.2 Exploratory Study Endpoint

**OA structural changes assessed by MRI**

- Cartilage volume loss from baseline (Visit 2) at D728 in the global knee and in the medial and lateral compartments.
- Change from baseline (Visit 2) at D728 in Bone Marrow Lesion (BML) score.
- Change from baseline (Visit 2) at D728 in synovitis (synovial membrane thickness).

**Signs and symptoms of OA**

- Change from baseline (Visit 2) in WOMAC Pain score at D728.
- Change from baseline (Visit 2) in WOMAC Stiffness and WOMAC function score at D182 and D728.
- Change from baseline (Visit 2) in Visual Analogue Pain Scale (VAS - Huskisson's) at D182 and D728.
- Percentage of OARSI (Osteoarthritis Research Society International) responders at D182 and D728.
- Percentage of patients with joint swelling and effusion at D182 and D728.
- Percentage of patients consuming rescue medication at D182 and D728.
- Change from baseline (Visit 2) in Patient's global assessment of disease activity at D182 and D728.
- Change from baseline (Visit 2) in Investigator's global assessment of disease activity at D182 and D728.
- Patient's global assessment of response to therapy at D182 and D728.
- Investigator's global assessment of response to therapy at D182 and D728.
- Change from baseline (Visit 2) in Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from the SF-36 at D182 and D728.

### 4.5.3 Safety Evaluation

- Incidence of adverse events
- Laboratory tests
- Vital signs

## 5. TRIAL TREATMENTS

### 5.1 Treatments Administered

Patients in the Diacerein group (n = 200) will take orally 50 mg once daily (1 capsule/day) in the evening for one month and 50 mg twice daily (morning and evening) thereafter for the duration of the study (182 or 728 days), always with meals.

Patients in the Celecoxib group (n = 200) will take one Celecoxib 200 mg capsule once daily orally in the morning for the whole duration of the study, always with meals.

Placebo: One capsule once daily in the evening in the Celecoxib group and one capsule once daily in the morning in the Diacerein group only the first months.

### 5.2 Identity of Study Products

**<u>Diacerein Group</u> (n = 200 patients)**

**Diacerein, 50 mg hard gelatine capsule**
Active ingredients: Diacerein 50 mg
Excipients: lactose monohydrate (214.3 mg), croscarmellose sodium (11.5 mg), polyvidone K30 (11.5 mg), colloidal silicon dioxide (11.5 mg) and magnesium stearate (1.2 mg)
Pharmacotherapeutic group: Other anti-inflammatory and antirheumatic agents, non-steroids.
Anatomical Therapeutic Chemical (ATC) code: M01 AX
Pharmaceutical form: Hard gelatine capsules
Dosage: one 50 mg capsule with the evening meal for the first 28 days (first month) of treatment, then twice daily morning (breakfast) and evening (dinner) for the next 5 or 23 months (total dose of 100 mg)
Route of administration: Oral
Special precautions for storage: 15-25°C
Manufacturer: Klocke Pharma Service, Strassburgerstrasse 77, 77767 Appenweier, Germany

**<u>Celecoxib Group</u> (n = 200 patients)**

**Celebrex®, 200 mg capsule (or generic)**
Active ingredient: Celecoxib, 200 mg
Excipients: croscarmellose sodium, lactose monohydrate, sodium lauryl sulphate, polyvidone and magnesium stearate
Pharmacotherapeutic group: Coxibs.
ATC code: M01AH
Pharmaceutical form: Hard gelatine capsules
Dosage: one 200 mg capsule once daily in the morning (breakfast) for 6 or 24 months.
Route of administration: Oral
Special precautions for storage: 15-25°C
Manufacturers:
Pfizer Canada, 17300 Trans-Canada Highway, Kirkland, Québec H9J 2M5, Canada
Apotex Inc., 150 Signet Drive, Toronto, Ontario, M9L 1T9, Canada

**<u>Placebo</u>**
Pharmaceutical form: Hard gelatine capsules filled with the excipients of Diacerein capsule.
Route of administration: Oral once daily in the morning (with breakfast) (only for the first 28 days of treatment in the Diacerein group) and once daily in the evening (dinner) in the Celecoxib group.
Special precautions for storage: 15-25°C
Manufacturer: Klocke Pharma Service, Strassburgerstrasse 77, 77767 Appenweier, Germany

### 5.3 Packaging and Labelling of Study Products

All the packaging and labelling procedures will be conducted by Ropack Inc., Montreal, Quebec, Canada for Canadian part of the study and by CSM Europe SA, Belgium, for the European part.

Study treatment will be packaged in boxes of 5 blisters containing 7 days of treatment per blister (i.e., 35 days of medication) including: one capsule of study product and one placebo capsule for the Celecoxib group; one capsule of study product and one placebo capsule for the first 28 days, or two capsules of study product thereafter, for the Diacerein group. The capsule to be taken in the morning will be distinguished from the capsule to be taken in the evening by a specific iconography (a sun and a moon, respectively).

### 5.4 Storage, Dispensing and Product Accountability

The treatments must be stored in a dry, secured area, between 15-25°C and will be under the direct responsibility of the investigator at study site.

Study treatments will be dispensed by the Investigator or his/her designee at Visit 2 (D0), Visit 3 (D60), and Visit 4 (D120) (Symptom study). Study treatments will be also dispensed at Visit 5 (D182), Visit 7 (D364) and Visit 9 (D546) in patients pre-selected for the 24-month study (MRI structural study).

The investigator is required to keep appropriate documentation of the delivery, use and the return of unused, used or partially used packages of investigational products. The documentation must include dates, quantities, patient numbers, batch/serial numbers or other identification number, expiry dates and the means to identify the patient to whom it was given.

All treatments supplied by the Sponsor and given to the Investigator (investigational product, comparator product, placebo and rescue medication) must be adequately accounted for during periodic monitoring visits as the study progresses and any unused study products must be returned to the Sponsor at the end of the study (upon request). All investigational medicine product and rescue medication, used or unused, could be destroyed at the end of different study parts (6 or 24 months) after the freezing of the database and confirmation by the Sponsor.

All documents proving the dispensation/recuperation/final destruction of the treatments will be returned to the Sponsor at the end of the study.

### 5.5 Treatment Compliance

At each visit after inclusion (Visit 2, D0), the patient will be asked to bring back the boxes and blisters of the test product and acetaminophen used during the previous study period. The clinical centres will verify the treatment compliance by counting the number of tablets left from the previous visit and will document these quantities in the source documents as well as in the appropriate section of the electronic Case Report Form (e-CRF).

Patient compliance with study medication intake will be assessed at each study visit (through patient interview and accountability of drug dispensed/retrieved) and recorded in the e-CRF. Patients will be regarded as compliant if the calculated compliance is at least 75% of the study medication required to be taken during the study, unless a dose is withheld due to adverse events or other unavoidable reasons (requires approval by the Investigator). Patients deemed to be non-compliant will be withdrawn from the study and the End of Study Form will be filled out.

## 5.6 Rescue Medication

If the patient is experiencing pain, acetaminophen, dosed at 500 mg, is authorised up to 2 g per day, i.e., 4 tablets per day. Acetaminophen must be interrupted 48 hours preceding each follow-up visit. Use of all such rescue medication must be recorded on the e-CRF.

Acetaminophen will be provided by the Sponsor to the investigator at the study site and dispensed by the investigator or his/her designee based on the maximal authorised doses (4 tablets/day) at Visit 2 (D0), Visit 3 (D60), and Visit 4 (D120) (Symptom study). Acetaminophen will be also dispensed at Visit 5 (D182), Visit 7 (D364) and Visit 9 (D546) in patients pre-selected for the 24-month study (MRI structural study). Rescue analgesia with acetaminophen must be interrupted 48 hours preceding each follow-up visit (Visits 2, 3, 4, 5, 7, 9 and 10).

## 5.7 Concomitant Treatments

### 5.7.1 Authorised Medications During the Study

Other rescue analgesia with narcotics will be authorised for a maximum of 3 days a month for treatment of pain related to the target knee or any other painful condition for which it is the physician's judgement that such treatment is indicated. NSAIDs are not allowed as rescue medication. Narcotics must be interrupted 1 week preceding each follow-up visit (Visits 2, 3, 4, 5, 7, 9 and 10).

Any other pre-existing treatment may be continued throughout the study. The concomitant treatments will be documented at the time of inclusion in the study. If, for any reason, modifications in the procedure are necessary, the new therapeutic modalities as well as the new treatments will be documented, and the information recorded in the e-CRF.

Patients may, at the Investigator's discretion, take a Proton Pump Inhibitor (PPI) or antacids daily as required, with at least a 2 hours interval from the intake of the study medication. This will be recorded in the e-CRF.

If treatment of osteoporosis (bisphosphonates, Selective Estrogen Receptor Modulator (SERMS), Thyroid-Stimulating Hormone (TSH)) is already prescribed, it will have to be continued, unmodified, for the entire duration of the study.

### 5.7.2 Unauthorised Medication During the Study

Patients are not allowed to take/use the following medication during the course of the study:

1. Corticosteroids (oral, injectable; exception of intra-articular/soft tissue injection at the exclusion of the target knee), indomethacin, therapeutic dose of glucosamine, chondroitin sulphate or Avocado-Soybean Unsaponifiables (ASU) (intra-articular injections of corticosteroids in the contralateral knee is allowed during the study);
2. Hyaluronic acid (intra-articular, target knee);
3. Natural health products (e.g. capsaicin, boswellia, willow bark), creams or analgesic gels (e.g. camphor and alcohol-based gels);
4. Natural health products susceptible to increase the risk of bleeding (e.g. garlic, dong quai, etc.);
5. Compounds containing non-approved agents for arthritis or agents claiming to possess disease/structure-modifying properties;
6. Medications with MMP-inhibitory properties (e.g. tetracycline or structurally related compounds);

7. Laxative, lithium carbonate, phenytoin or anticoagulants (with the exception of acetyl salicylic acid [ASA] up to a maximum daily dose of 325 mg);
8. Oral or topical coxibs;
9. Calcitonin;
10. Immunosuppressive drugs.

# 6. TRIAL VISITS

## 6.1 Flow Charts

Flow charts of study assessments for the 182-day symptom study and the 728-day MRI structural study are presented in Section 6.1.1 and 6.1.2, respectively.

### 6.1.1 Time and Events Schedule (182 days Symptom Study)

| Visits | Pre-treatment period | | Treatment period | | |
|---|---|---|---|---|---|
| | Screening | Inclusion (Randomisation) | Clinic Visit | Clinic Visit | End of Study/Early Termination Visit |
| | D-30 - D0 **Visit 1** | D0 **Visit 2** | D60±3 **Visit 3** | D120±7 **Visit 4** | D182±7 **Visit 5** |
| Informed consent | X | | | | |
| Inclusion/exclusion criteria | X | X | | | |
| Medical and surgical history and related medications | X | | | | |
| Demographic information | X | | | | |
| Knee X-ray (weight-bearing) | X[1] | | | | |
| Physical examination and blood pressure | X | | | | X |
| Electrocardiogram (ECG) | X | | | | |
| Assessment of knee joint | X | X | X | X | X |
| ACR Criteria for knee OA | X | | | | |
| Blood sample (haematology, etc.) | X | | X | X | X |
| Dispensation of study treatment[2] and acetaminophen | | X | X | X | |
| VAS pain* | X | X | X | X | X |
| WOMAC* | | X | X | X | X |
| SF-36* | | X | X | X | X |
| Compliance to study medication and acetaminophen | | | X | X | X |
| Concomitant medications | | X | X | X | X |
| Recording of acetaminophen use | | | X | X | X |
| Adverse Events (AE) assessment | | X | X | X | X |
| Information on referral for knee arthroplasty | | X | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| Patient and investigator global assessment of disease activity | | X | X | X | X |
| Patient and investigator global assessment of response to therapy | | | X | X | X |

[1]If not done within 12 months; [2]This study is double blinded

*All self-reporting questionnaires will be provided to patient in local language.

### 6.1.2 Time and Events Schedule (728 days MRI Structural Study)

| Visits | Pre-treatment period | | Treatment period | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Inclusion (Randomi-sation) | Clinic Visit | Clinic Visit | Clinic Visit | ☎ Visit | Clinic Visit | ☎ Visit | Clinic Visit | End of Study/Early Termination Visit |
| | D-30 - D0 **Visit 1** | D0 **Visit 2** | D60±3 **Visit 3** | D120±7 **Visit 4** | D182±7 **Visit 5** | D273±7 **Visit 6** | D364±15 **Visit 7** | D455±7 **Visit 8** | D546±7 **Visit 9** | D728±15[6] **Visit 10** |
| Informed consent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Medical and surgical history and related medications | X | | | | | | | | | |
| Demographic information | X | | | | | | | | | |
| Knee X-ray (weight-bearing) | X[1] | | | | | | | | | |
| Physical examination and blood pressure | X | | | | X | | X | | | X |
| ECG | X | | | | | | | | | |
| Assessment of knee joint | X | X | X | X | X | | X | | X | X |
| ACR Criteria for knee OA | X | | | | | | | | | |
| Blood sample (haematology, etc.) | X | | X | X | X | | X | | X | X |
| Serum sample (biomarker analysis) | | X | | | | | X | | | X |
| Dispensation of study treatment[2] and acetaminophen | | X | X | X | X | | X | | X | |
| MRI of the knee[3] | | X | | | | | X[4] | | | X[5,6] |

| Visits | Screening | Inclusion (Randomisation) | Clinic Visit | Clinic Visit | Clinic Visit | ☎ Visit | Clinic Visit | ☎ Visit | Clinic Visit | End of Study/Early Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| | D-30 - D0 **Visit 1** | D0 **Visit 2** | D60±3 **Visit 3** | D120±7 **Visit 4** | D182±7 **Visit 5** | D273±7 **Visit 6** | D364±15 **Visit 7** | D455±7 **Visit 8** | D546±7 **Visit 9** | D728±15 **Visit 10** |
| VAS pain* | X | X | X | X | X | | X | | X | X |
| WOMAC* | | X | X | X | X | | X | | X | X |
| SF-36* | | X | X | X | X | | X | | X | X |
| Compliance to study medication and acetaminophen | | | X | X | X | | X | | X | X |
| Concomitant medications | | X | X | X | X | X | X | X | X | X |
| Recording of acetaminophen use | | | X | X | X | X | X | X | X | X |
| AE assessment | | X | X | X | X | X | X | X | X | X |
| Information of referral for knee arthroplasty | | X | X | X | X | X | X | X | X | X |
| Patient and investigator global assessment of disease activity | | X | X | X | X | | X | | X | X |
| Patient and investigator global assessment of response to therapy | | | X | X | X | | X | | X | X |

[1]If not done within 12 months
[2]This study is double blinded
[3]MRI will only be performed if the patient is eligible to study criteria other than those related to MRI procedure/analysis, as close as possible to the Inclusion Visit.
[4]MRI to be performed between D349 and D379
[5]MRI to be performed between D713 and D743
[6]In the event of a premature withdrawal from the study, patients will be invited to have a 24-month MRI performed as if they had completed the entire study in accordance to protocol.

*All self-reporting questionnaires will be provided to patient in local language.

### 6.2 Visit 1 (Screening Visit) (D-30 – D0)

The screening visit (Visit 1) allows an assessment of patients who are susceptible of being randomised into the study.

Allocation of the patient identification number. Each patient will be identified by a 5-digit selection number: the first digit will indicate the country (0 or 5 for Canada, 1 for Spain, 2 for Austria, 3 for Czech Republic and 4 for Belgium), the second digit will identify the investigation centre (1 to x by country) and the three last, corresponding to the chronological entry order of the patient in the study of that specific centre (by increasing order, i.e. 001, 002, etc.). The first selected patient in Canada centre 1 will therefore be allocated the selection number 01-001. The following patients will subsequently be assigned the selection numbers 01-002, 01-003, etc.

The Investigator must have the patient signed *Patient Consent Form* before any procedure concerning the study can be initiated. A copy, also signed by the investigator, will be given to the patient. He must verbally describe to the potential patient all aspects of the study, explain the aims that are being sought and inform him/her about the possible benefits and risks. The Investigator must give him/her the documentation intended for the patient and discuss the information in comprehensible terms. For patients included in the 728-day MRI structural study, a separate *MRI Patient Consent Form* must be completed and signed, in two copies, by both the patients and the investigators.

The investigator must verify the criteria of inclusion and non-inclusion (see details in Section 8) and collect all information related to the study.

The following assessments/procedures will be completed and the information will be collected and reported in the e-CRF:

- Identification of the patient;
- Inclusion and non-inclusion criteria (verified);
- History of gastro-intestinal (GI) diseases or history of diarrhoea;
- Medical information including the demographic data and determination of body mass index (BMI), medical and surgical history, related treatments and, in particular, the unauthorised treatments before and/or during the study;
- Physical examination, blood pressure and ECG;
- Patients who have significant risk factors for heart attack or stroke will be assessed carefully. Risk factors for heart attack and stroke include high blood pressure (treated or untreated), high cholesterol, diabetes and smoking. The global risk assessment will be assessed using the American Heart Association (AHA) assessment of CV risk tables (see Appendix VII A) [23]. Patients with high risk of CV events (see Appendix VII B) will be excluded;
- Recording of pain assessment score (VAS 0-100 mm) while walking on a flat surface (≥ 40 mm) (See Appendix IV);
- Classification of knee OA according to ACR criteria;
- Assessment of joint swelling, effusion, or both;
- For post- or perimenopausal women with at least one (1) year of confirmed amenorrhea, a blood level of Follicule-Stimulating Hormone (FSH);
- Blood tests: haematology profile, sedimentation rate at 1 hour (SR), C-reactive protein (CRP), liver function test (Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], Alkaline phosphatase [ALP], bilirubin), renal function test (urea, creatinine, electrolytes); and (if not made within the last 6 months): glucose, total cholesterol, Low

Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and triglycerides after a 12-hour fast;
- Lastly, scheduling the Inclusion Visit (Visit 2) no more than 30 days later.

If the patient has no weight-bearing X-rays of the target knee taken in the previous 12 months, a radiological assessment will be required in order to verify that the patient satisfies radiological criteria for inclusion.

Following assessment, the physician will inform the patient of his/her inclusion in or exclusion from the study and of the modalities regarding the continuation of the study. The physician will also explain to the patient the modalities of the treatment, and review the unauthorised treatments during the study.

The patients included in the 728-day MRI structural study will be subsequently referred for MRI evaluation of the studied knee, as close as possible to the Inclusion Visit date. The patients must undergo this examination in order to ensure eligibility. Patient eligibility will be reviewed within 48 hours from receiving patient knee images by a central reading laboratory (ArthroLab Inc., 1871 Sherbrooke Street East, Montreal, Quebec).

If a selected patient becomes ineligible for the study, his/her selection number will not be reallocated to another patient.

### 6.3 Visit 2 (Inclusion Visit) (D0)

If all the inclusion criteria are satisfied and the patient does not have any exclusion, he/she can be included in the study. After verifying that the washout period has been respected regarding the use of NSAIDs (7 days) and acetaminophen or paracetamol (48 hours), the following procedures/assessments will be completed and the information will be collected and reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 30-day screening period)):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface (≥ 40 mm);
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient (See Appendix V);
- Completion of the SF-36 questionnaire by the patient (See Appendix VI);
- Patients' and investigators' global assessment of disease activity (See Appendix VIII and Appendix IX)
- Assessment of joint swelling, effusion, or both;
- Recording of analgesic and anti-inflammatory drug use, and any other concomitant medication;
- Dispensing the study medication according to the randomisation;
- Dispensing of the acetaminophen;
- Adverse events recording and assessment;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Collection of blood samples for the measurement of biomarkers in the serum **(728-day MRI structural study only);**
- Lastly, scheduling the follow-up visit (Visit 3) 60 days later ± 3 days.

Patients will have to return the packaging of the used study medications as well as the unused study medications at each study visit.

### 6.4 Visit 3 (60 ± 3 Days of Treatment)

After verifying that the washout period has been respected regarding the use of acetaminophen (48 hours) the following procedures/assessments will be completed and the information will be collected and reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 7-day window) or declared a minor protocol deviation):

- Recording of pain assessment score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- Completion of the SF-36 questionnaire by the patient;
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Recording of acetaminophen use since the last visit;
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Dispensing the study medication according to the randomisation;
- Dispensing acetaminophen;
- Adverse events assessment;
- Patients' and investigators' global assessment of disease activity (See Appendix VIII and Appendix IX)
- Patients' and investigators' global assessment of response to therapy
- Concomitant medication recording;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, scheduling the follow-up visit 120 days (± 7 days) after Inclusion Visit (D0).

### 6.5 Visit 4 (120 ± 7 Days of Treatment)

After verifying that the washout period has been respected regarding the use of acetaminophen (48 hours) the following procedures/assessments will be completed and the information will be collected and reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 15-day window) or declared a minor protocol deviation):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- -Completion of the SF-36 questionnaire by the patient;
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Recording of acetaminophen use since the last visit;
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Dispensing study medication according to the randomization;
- Dispensing acetaminophen;
- Adverse events assessment;
- Patients' and investigators' global assessment of disease activity;

- Patients' and investigators' global assessment of response to therapy;
- Concomitant medication recording;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, scheduling the follow-up visit (Visit 5) 182 days (± 7 days) after Inclusion Visit (D0).

### 6.6 Visit 5 (End of Study or Early Termination, 182 ± 7 Days of Treatment) for Study Centres Not Involved in the 2-years Structural Study

**IF THE PATIENT HAS BEEN SELECTED FOR THE MRI-STRUCTURAL STUDY GO TO NEXT SECTIONS**

After verifying that the washout period (48 hours) has been respected, or not, regarding the use of acetaminophen, the following procedures/assessments will be completed and the information will be reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 15-day window) or declared a minor protocol deviation):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- Completion of the SF-36 questionnaire by the patient;
- Physical examination, blood pressure (blood pressure will only be recorded in source documents);
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Recording of acetaminophen use since the last visit;
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Adverse events assessment;
- Patients' and investigators' global assessment of disease activity
- Patients' and investigators' global assessment of response to therapy (See Appendix X and Appendix XI)
- Concomitant medication recording;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, the *End of Study Form* will be completed by the Investigator or his/her designee;

## THE FOLLOWING VISITS RELATE ONLY TO PATIENTS INCLUDED IN THE 728-DAY MRI STRUCTURAL STUDY

### 6.7 Visit 5 (182 ± 7 Days of Treatment) for Study Centres Involved in the 2-years Structural Study

After verifying that the washout period has been respected regarding the use of acetaminophen (48 hours) the following procedures/assessments will be completed and the information will be collected and reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 15-day window) or declared a minor protocol deviation):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- Completion of the SF-36 questionnaire by the patient;
- Physical examination and blood pressure (blood pressure will only be recorded in source documents);
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Recording of acetaminophen use since the last visit;
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Dispensing of study medication according to the randomisation;
- Dispensing of the acetaminophen;
- Adverse events assessment;
- Patients' and investigators' global assessment of disease activity;
- Patients' and investigators' global assessment of response to therapy;
- Concomitant medication recording;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, scheduling the follow-up phone call (Visit 6) 273 days (± 7 days) after Inclusion Visit (D0).

### 6.8 Visit 6 (273 ± 7 Days of Treatment) (Phone Contact)

A phone call to the patient in order to inquire about the evolution of the study and answer questions the patient might have. The information will be collected and reported in the e-CRF:

- Adverse events assessment;
- Concomitant medication recording;
- Recording of acetaminophen use since the last visit;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, scheduling the next visit (Visit 7) 364 days (± 15 days) after Inclusion Visit (D0).

### 6.9 Visit 7 (364 ± 15 Days of Treatment)

After verifying that the washout period (48 hours) has been respected regarding the use of acetaminophen, the following procedures/assessments will be completed and the information will be reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 31-day window) or declared a minor protocol deviation):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- Completion of the SF-36 questionnaire by the patient;
- Physical examination and blood pressure (blood pressure will only be recorded in source documents);
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Collection of blood samples for the measurement of biomarkers in the serum;
- Recording of acetaminophen use since the last visit;
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Dispensing of study medication according to the randomisation;
- Dispensing of the acetaminophen;
- Adverse events assessment;
- Patients' and investigators' global assessment of disease activity;
- Patients' and investigators' global assessment of response to therapy;
- Concomitant medication recording;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- The appointment date for the second MRI examination of the knee (between D349 and D379) will be confirmed with the patient;
- Lastly, scheduling the follow-up phone call (Visit 8) 455 days (± 7 days) after Inclusion Visit (D0).

### 6.10 Visit 8 (455 ± 7 Days of Treatment) (Phone Contact)

A phone call to the patient to inquire about the evolution of the study and answer questions the patient might have. The information will be collected and reported in the e-CRF:

- Adverse events assessment;
- Concomitant medication recording;
- Recording of acetaminophen use since last visit;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, scheduling the next visit (Visit 9) 546 days (± 7 days) after Inclusion Visit (D0).

### 6.11 Visit 9 (546 ± 7 Days of Treatment)

After verifying that the washout period (48 hours) has been respected regarding the use of acetaminophen, the following procedures/assessments will be completed and the information will be reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 15-day window) or declared a minor protocol deviation):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- Completion of the SF-36 questionnaire by the patient;
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Recording of acetaminophen use since the last visit;
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Dispensing of study medication according to the randomisation;
- Dispensing of the acetaminophen;
- Adverse events assessment;
- Patient and investigator global assessment of disease activity
- Patients' and investigators' global assessment of response to therapy
- Concomitant medication recording;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Lastly, scheduling the next visit 728 days (±15 days) after Inclusion Visit (D0).

### 6.12 Visit 10 (End of Study Visit or Early Termination, 728 ± 15 days of treatment)

After verifying that the washout period (48 hours) has been respected regarding the use of acetaminophen, the following procedures/assessments will be completed and the information will be reported in the e-CRF (In case the washout is not respected, the investigator can postpone the visit (in respect of the 31-day window) or declared a minor protocol deviation):

- Recording of pain score (VAS 0-100 mm) while walking on a flat surface;
- Recording of WOMAC index data [score 0-240] (Section A: Pain [score 0-50], Section B: Stiffness [score 0-20], Section C: Function [score 0-170]) to be completed by the patient;
- Completion of the SF-36 questionnaire by the patient;
- Recording of acetaminophen use since the last visit;
- Physical examination, blood pressure (blood pressure will only be recorded in source documents);
- Assessment of joint swelling, effusion or both;
- Blood tests: haematology profile, SR, CRP, liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes);
- Collection of blood samples for the measurement of biomarkers in the serum;
- Recording information on referral for knee arthroplasty (this will only be recorded in source documents);
- Verification of the dispensed study medication according to the randomisation;
- Verification of the dispensed acetaminophen;
- Adverse events assessment;
- Patients' and investigators' global assessment of disease activity;
- Patients' and investigators' global assessment of response to therapy;
- Concomitant medication recording;
- The appointment date for the third MRI examination of the knee (between D713 and D743) will be confirmed with the patient;

- Lastly, the *End of Study Form* will be completed by the Investigator or his/her designee.

### 6.13 Early Termination

In the event of premature discontinuation from the study, for any reason, the Investigator or his/her designee will try to collect all the information related to the End of Study visit and the *End of Study Form* must be competed.

In addition, **for the MRI-structural study only**, patients will be invited to have a 24-month MRI performed as if they had completed the entire study in accordance to protocol. The *End of Study Form* should also be completed for patients with a premature discontinuation of the study.

### 6.14 End of Trial

The trial will be considered closed after the last patient has completed its last, planned, trial-related visit.

## 7. ASSESSMENT OF EFFICACY

The VAS, WOMAC index, and SF-36 data collected in this study will be collected on the supplied, printed, questionnaire which will be considered source documentation and will not be subjected to duplication (i.e., will not be recorded in the patient's medical notes).

### 7.1 Assessment of the OA Symptoms

Functional disability will be assessed by the patients using the WOMAC which is a validated index recognised as the standard for the assessment of knee OA (pain, function and stiffness). The WOMAC index (Version VA 3.0) questionnaire is administrated at Inclusion Visit (Visit 1), and at each follow-up visit at the investigation centre.

The WOMAC index includes 24 items grouped into three subscales: pain (section A, 5 items), stiffness (section B, 2 items) and physical function activities (section C, 17 items). Each item is a 10 cm VAS with 0 and 10 cm representing no pain/difficulty and extreme pain/difficulty respectively.

### 7.2 Assessment of Knee Joints

Knee joint (Joint swelling, effusion or both) will be assessed at Screening (Visit 1), at Inclusion Visit (Visit 2, D0), and at each follow-up visit at the investigation centre.

### 7.3 Patient's and Investigator's Global Assessments of Disease Activity

The global assessment of disease activity will be assessed separately by the patients and by the investigators at inclusion Visit (Visit 2, D0) and each follow-up visit at the investigation centre using a VAS.

### 7.4 Patient's and Investigator's Global Assessments of Response to Therapy

The global assessment of response to therapy will be assessed separately by the patients and by the investigators at inclusion Visit (Visit 2, D0) and each follow-up visit at the investigation centre using a VAS.

### 7.5 Assessment of Quality of Life

The SF-36 questionnaire will be administered to patients at Inclusion Visit (Visit 2, D0), and at each follow-up visit at the investigation centre.

### 7.6 Assessment of the OA Structural Changes by MRI (MRI-Structural Study Only)

The sub-population of patients who have undergone MRI exams (100 preselected patients from approximately 4 Canadian centres) will be subjected to the following analyses:

The cartilage volume loss will be evaluated by the central reading laboratory in the medial and lateral compartments and the global knee, its subregions and the femoral condyles and tibial plateaus using a fully automated software [19-21].

The severity of synovitis will be evaluated in four regions of interest (ROIs) in the images of the axial T1-weighted acquisition complemented with the use of the images of the axial T2-weighted acquisition as described by Pelletier [24]. The thickness of the synovial membrane will be evaluated in the global knee and each ROIs.

A quantitative evaluation of the volume of synovial fluid in the osteoarthritic knee will be made using a fully automated method and reported in millilitre (ml) [25].

The bone marrow lesions (BMLs) will be assessed and quantified in the different sub regions of the knee by a fully automated method [26] as follows:

The presence of a meniscal extrusion will be assessed, on the baseline MRI only, using a semi-quantitative scoring system [27] in each of the three subregions, i.e. anterior horn, body, and posterior horn, of the lateral and medial menisci. The absence of an extrusion in all the subregions will be considered as an absence (score = 0) of extrusion in the meniscus. The presence of an extrusion in at least one region of the meniscus will be sufficient to consider the presence (score = 1) of extrusion in the meniscus [27]. Meniscal extrusion may also be scored using a fully automated technology.

### 7.7 Assessment of Biomarkers (MRI-structural study only)

Blood samples will be collected from each patient at Visit 2 (Inclusion), Visit 7 (D364), and Visit 10 (D728) (or Early Termination Visit). These samples will be frozen and stored until the end of the study and batch-shipped to the laboratory designated by the Sponsor for biomarker analysis. Ideally, samples will be stored at -80˚C but could be stored at -20˚C until analysis. It will be decided at the end of the study which biomarkers will be useful to measure.

### 7.8 Assessment of Safety

Safety will be assessed by recording all adverse events at each post-screening visit.

Clinical laboratory tests will be assessed and recorded at Visit 1 (Screening), Visit 3 (D60), Visit 4 (D120) and, Visit 5 (D182), and at Visit 7 (D364), Visit 9 (D546), and Visit 10 (D728).

Blood pressures will be assessed and recorded on source document at Visit 1 (Screening), Visit 5 (D182), Visit 7 (D364), and Visit 10 (D728).

Clinical examination will be performed and recorded at Visit 1 (Screening), Visit 5 (D182), Visit 7 (D364), and Visit 10 (D728).

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

## 8.1 Inclusion Criteria

1. Men and women of at least 50 years of age;
2. Patients followed in an ambulatory clinic;
3. Patients presenting primary OA of the knee according to ACR criteria;
4. Patients with OA of radiological stages 2 and 3 according to Kellgren-Lawrence;
5. Patients with a minimum joint space width ≥2 mm in the medial tibio-femoral compartment on standing knee X-ray **(MRI structural study only)**;
6. Patients with knee pain on most days of the month before entering into the study;
7. Patients with a VAS pain score (0-100 mm) while walking on a flat surface ≥ 40 mm (Visit 1 (Screening)and Visit 2 (Inclusion Visits));
8. Patients with no clinically significant laboratory abnormalities in the judgment of the investigator;
9. Female patients who are post or perimenopausal with confirmed amenorrhea for at least one year before entering this study must agree to have a blood level of FSH at Screening visit. Female patients having had tubal ligation, bilateral oophorectomy or hysterectomy are recognized as sterile and can be included in the study without the need for FSH testing;
10. Patients agreeing to sign the *Informed Consent Form* prior to any study-related activities after having been clearly informed of its methods and constraints;
11. Patients not taking part in another clinical study;
12. Patients agreeing to respect the protocol by attending the visits related to the study.

## 8.2 Exclusion Criteria

### 8.2.1 Criteria Related to Individual Characteristics of the Patient

1. Patients with secondary knee OA;
2. Patients with known hypersensitivity to Diacerein or to anthraquinone-containing product, hypersensitivity to Celecoxib, who have demonstrated allergic-type reactions to sulphonamides, experienced asthma, urticaria or allergic-type reactions after taking sulphonamides, aspirin (acetyl salicylic acid [ASA]), lactose, NSAIDs, acetaminophen or paracetamol;
3. Patients with a known history of diarrhoea, more particularly if 65 years of age and older;
4. Patients with active malignancy of any type or history of a malignancy within the last five years other than basal cell carcinoma;
5. Patients with other bone and articular diseases (antecedents and/or current signs) such as chondrocalcinosis, Paget's disease of the ipsilateral limb to the target knee, rheumatoid arthritis, aseptic osteonecrosis, gout, septic arthritis, ochronosis, acromegaly, haemochromatosis, Wilson's disease, osteochondromatosis,

seronegative spondylo-arthropathy, mixed connective tissue disease, collagen vascular disease, psoriasis, inflammatory bowel disease;

6. Pain in other parts of the body greater than the knee pain that could interfere with the evaluation of the index joint;
7. Patients with fibromyalgia;
8. Patients with isolated knee lateral compartment OA defined by joint space loss in the lateral compartment only;
9. Patients with Class IV functional capacity using the American Rheumatism Association criteria;
10. Patients who have had surgery in any lower limb or arthroscopy, aspiration or lavage in any lower limb joint within 180 days of the Inclusion Visit (Visit 2);
11. Patients who have had meniscal surgery on the study knee;
12. Patients who have undergone total knee replacement in the contralateral knee within 182 days prior to the Screening Visit (Visit 1);
13. Patients with co-morbid conditions or joint deformity that restrict knee function;
14. Patients with a history of heart attack or stroke, or who have had serious diseases of the heart such as congestive heart failure (functional classes II-IV of the NYHA);
15. Patients who have significant risk factors for heart attack or stroke will be assessed carefully. Risk factors for heart attack and stroke include high blood pressure (treated or untreated), high cholesterol, diabetes and smoking. The global risk assessment will be assessed using the American Heart Association (AHA) assessment of CV risk tables (see Appendix VII A) [23]. Patients with high risk of CV events (see Appendix VII B) will be excluded;
16. Patients with any significant diseases or conditions, including emotional or psychiatric disorders and substance abuse that, in the opinion of the Investigator, are likely to alter appreciation of OA symptoms or the patient's ability to complete the study;
17. Patients with a history of any illness that, in the opinion of the Investigator, might confound the results of the study or pose additional risk to the patient;
18. Patients with poorly controlled diabetes mellitus defined as Haemoglobin A1c level >8%;
19. Patients with poorly controlled hypertension (sustained Systolic Blood Pressure of >150 mmHg or Diastolic Blood Pressure >95 mmHg);
20. Patients with any active acute or chronic infections requiring antimicrobial therapy, or serious viral (e.g., hepatitis, herpes zoster, human immunodeficiency virus (HIV) positivity) or fungal infections;
21. Patients with a history of recurrent upper gastrointestinal tract (UGI) ulceration or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), a significant coagulation defect, or any other condition, which in the investigator's opinion might preclude the chronic use of Celecoxib or Diacerein. Patients may, at the Investigator's discretion, take a PPI or antacids daily as required, with a 2 hour period between intake of study medication and intake of PPI or antacid;
22. Patients who have been diagnosed as having or have been treated for oesophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication;
23. Patients with chronic liver or kidney disease, as defined by AST or ALT >2.0 times the upper limit of normal (ULN) or blood urea nitrogen (BUN) or serum creatinine >2.0 times ULN, at the Screening Visit (Visit 1);

24. Patients who have a history of intolerance to acetaminophen or paracetamol, opioids or opioid combinations such that it is felt that an adequate non-anti-inflammatory rescue analgesic regimen cannot be safely prescribed;
25. Patients who have a history of alcohol or substance abuse within the last 3 years;
26. Patients receiving any investigational drug within 30 days or 5 half-lives (whichever is greater) prior to the Inclusion Visit (Visit 2);
27. Patients who plan surgery during the study;
28. Female patients who are breastfeeding;
29. Patients with the impossibility of taking part in the total duration of the study and attending the visits;
30. Patients unable to give an informed consent;
31. Patients who do not respect the acetaminophen or paracetamol washout period of 48 hours or the NSAID washout period of 1 week before the Inclusion Visit (Visit 2).

### 8.2.2 Treatment-Related Exclusion

32. Patients using corticosteroids (oral, injectable; exception of intraarticular/soft tissue injection at the exclusion of the target knee), indomethacin, therapeutic dose of glucosamine, chondroitin sulphate or Diacerein or ASU during the 12 weeks preceding inclusion (intraarticular injections of corticosteroids in the contralateral knee is allowed during the study);
33. Patients using hyaluronic acid (intra-articular target knee) during the 26 weeks preceding inclusion;
34. Patients using natural health products (e.g., capsaicin, boswellia, willow bark), and creams and analgesic gels (e.g. camphor and alcohol-based gels) during one week preceding inclusion;
35. Patients using natural health products susceptible to increase the risk of bleeding (e.g. garlic, dong quai, etc.) during one-week preceding inclusion;
36. Patients receiving radioactive synovectomy (target knee) during the 12 weeks preceding inclusion;
37. Patients who are taking NSAIDs and do not want to stop during the study;
38. If treatment of osteoporosis (bisphosphonates, SERMS, TSH) is necessary, it will have to be continued, unmodified, for the entire duration of the study;
39. Patients who have used compounds containing non-approved agents for arthritis or agents claiming to possess disease/structure-modifying properties in the 14 days prior to the Inclusion Visit (Visit 2);
40. Patients who have used medications with MMP-inhibitory properties (e.g. tetracycline or structurally related compounds) within 28 days prior to the Inclusion Visit (Visit 2);
41. Patients who require acetaminophen or paracetamol at daily doses >2000 mg (2 g) on a regular basis;
42. Patients who are taking a laxative, lithium carbonate, phenytoin or anticoagulants (with the exception of ASA up to a maximum daily dose of 325 mg);
43. Patients who have received chondrocyte transplants or underwent other type of cartilage repair procedures in the target joint;
44. Patients who use oral or topical coxibs;
45. Patients who use calcitonin;
46. Patients who use immunosuppressive drugs.

### 8.2.3 Criteria Related to Magnetic Resonance Imaging (MRI)

47. Patients presenting a counter-indication to an MRI examination;
48. Patients whose Inclusion Visit cartilage volume cannot be calculated from the MRI due to advanced OA disease;
49. Patients whose Inclusion Visit cartilage volume cannot be calculated from the MRI due to the presence of large fat pads or any other technical reason;
50. Patients with study knee not entering in the MRI magnet;
51. Patients with abnormal Inclusion Visit findings and/or any other condition, which, in the Investigator's judgment, might increase the risk to the patient or decrease the chance of obtaining satisfactory data through MRI to achieve the objectives of the study.

## 8.3 Randomisation Procedures

The treatments will be allocated according to a predefined randomisation scheme using a mathematical algorithm.

A total of approximately 400 patients will be randomised to one of the 2 treatment groups in a 1:1 ratio. The randomisation number for each patient will be allocated at Visit 2 (Inclusion Visit) after verifying the inclusion and exclusion criteria.

The original randomisation list will be kept secured by Ropack until the study blind is broken after the end of the 6-months part of the study.

Approximately 100 out of the 400 patients from pre-identified investigative sites in Canada will be randomised to the MRI structural study and will be enrolled at the Inclusion Visit for the 24-month study.

At the investigational site, each randomised patient will be assigned a patient identification number. This number will be used on all patient documentation. Numbers are assigned in ascending sequential order. The patient randomisation number consists of three digits.

## 8.4 Blinding Procedures

This study is a double-blind study (the patients, Investigators, other investigator site personnel, and the Sponsor representative will not be aware of the randomisation). Blinding will be maintained by the following measures:

- The randomisation list will remain secret throughout the study and will be secured by Ropack. Two sets of individually sealed code envelopes will be established; one kept by PharmaLex GmbH, and the second intended for the Investigator.
- The test products and placebo capsules will be presented as identical capsules concerning the colour, size and shape and weight. They will be packed in identical blisters and these blisters will be placed in identical plain, carton boxes, bearing an identification label on the box and an iconography to distinguish the morning capsule (a sun) from the evening capsule (a moon).
- Patients in both groups will take the same number of capsules daily. Patients in the Diacerein group will take one capsule of Diacerein and one capsule of matching placebo for one month and then two capsules of Diacerein per day for the duration of the study to which they have been randomized. Patients in the Celecoxib group will take one capsule of Celecoxib and one capsule of a matching placebo.

Randomisation code envelopes for each patient will be provided to the Investigators. The sealed randomisation code envelopes must be kept in a secure area, accessible only to authorised study personnel and accessible at all times by the Investigator. The integrity of the randomisation codes will be ensured throughout the study by means of periodic inspections by the monitors. At the end of the study, all randomisation code envelopes will be collected by the monitors and must be returned to the Sponsor.

All analyses regarding the primary outcome measure of this study (non-inferiority of Diacerein compared to Celecoxib concerning the WOMAC pain reduction at 182 days), other outcome measures and patients' characteristics will be performed once all patients have completed the 6-month follow-up visit. The designated biostatistician responsible for these statistical analyses and the Sponsor will be receiving the information related to medication allocation for each patient, in order to be able to produce the analysis as described in the statistical plan and prepared the Clinical Study Report. The double-blind status will be maintained for all other parties (patients, investigator and site personnel) until completion of the study at 728 days.

Should the analysis of the primary outcome fails to confirm the non-inferiority of diacerein to celecoxib, the MRI Study will be discontinued.

### 8.5 Breaking Blinding Procedures

In the event of a medical emergency for which knowledge of the treatment assignment is required in order to provide the appropriate medical care to the patient, the Investigator may open the randomisation code envelope for that patient only. The date, hour and reasons for breaking the code as well as the name of the person who has broken the code must be written on the envelope and a detailed report must be appended to the e-CRF.

The Investigator will be authorized to open the code envelope, following consultation with ArthroLab Inc. (Dr. Jean-Pierre Pelletier or Mr. Patrice Paiement).

The patient for whom the code has been broken will be excluded from the study.

### 8.6 Duration of Therapy

The duration of the double-blind study will be 182 ± 7 days for all 400 patients included in the symptom study and 728 ± 15 days for approximately 100 patients, preselected from 4 investigative centres in Canada, identified at the time of inclusion and receiving randomisation numbers 001 to 100, in order to explore the DMOAD effect of Diacerein assessed by MRI. Procedures will be performed as per the schedule provided in the flow chart (Section 6).

### 8.7 Patient Withdrawal Criteria

As much as possible, the Investigator will try to maintain the patient in the study and every effort will be expended to obtain the related information at the end of the follow-up visit of the patient.

The patients have the right to withdraw from the study at any moment and for any reason.

The Investigator can also choose to remove a patient from the study if the study is judged to compromise the safety or well-being of the patient.

Patients who undergo a total knee replacement in the contralateral knee during the study will be considered withdrawn early. Patients who are part of the structural study will have to undergo an exit MRI evaluation. In any case, the Investigator or his/her designee will have to fill out the *End of Study Form*.

If the patient withdraws from the study, for any reason, before the end of the study, the *End of Study Form* in the e-CRF must be completed by the Investigator or his/her designee. The reasons for withdrawal from the study must be described and documented and in the case of multiple reasons, the main reason must be identified by the Investigator or his/her designee.

In the case of withdrawal due to Serious Adverse Events (SAE), the patient should be followed up until the disappearance or the stabilisation of the SAE. All adverse events must be documented, and the collected information reported in the e-CRF.

All premature withdrawals must be reported to the Sponsor or its representative. The randomised patients who withdraw from the study will not be replaced.

### 8.8 Study Termination

The Sponsor may, at any time, terminate the study or any part of the study for administrative, safety or regulatory reasons.

The Sponsor can choose to interrupt the study prematurely in a given centre for the following reasons:

- Major personnel changes in the centre or the organisation, which could adversely affect the recruitment, the quality of the study and the respect of Good Clinical Practice;
- Non-respect of the protocol resulting in major violations;
- Non-respect of Good Clinical Practice;
- Insufficient recruitment.

## 9 ASSESSMENT OF SAFETY

### 9.1 Specification of Safety Parameters

The safety endpoints in this study are described as:

- adverse events;
- laboratory tests: blood samples will be collected before study medication administration at screening and at 3, 4, 5, 7, 9 and 10 for laboratory safety analyses:

  **haematology**: CBC (RBC count, haemoglobin, haematocrit, WBC count plus differential count, platelet count, SR 1 hour).
  **routine blood chemistry**: C-reactive protein (CRP), liver function test (AST, ALT, ALP, bilirubin), renal function test (urea, creatinine, electrolytes).
- physical findings during general physical examination;
- recording of vital signs (weight, systolic/diastolic blood pressure).

Liver function will be monitored by measuring serum liver aminotransferases and total bilirubin at visits 3, 4, 5, 7, 9 and 10 (refer to Section 9.5).

## 9.2 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Events and Intercurrent Illnesses

### 9.2.1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Adverse events may include the following types of occurrences:

- suspected adverse drug reactions;
- other medical experiences, regardless of their relationship with Diacerein, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing or physical examination findings;
- reactions from study medication overdose, abuse, withdrawal, sensitivity, toxicity;
- AEs associated with clinical study procedures that could modify the conduct of the study.

Those medical conditions related to the disease under study whose changes during the study are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the study medication, are not considered AEs and should not be recorded in the e-CRF (Section 9.2.4). All other medical conditions which are present at baseline should not be considered AEs unless a worsening has occurred (Section 9.2.3).

Procedures such as diagnostic tests should not be recorded as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of AE.

In case of a fatality, the cause of death is considered as the AE, and the death as its outcome.

### 9.2.2 Abnormal Laboratory Findings and Other Objective Measurements

Abnormal laboratory findings and other objective measurements should NOT be routinely recorded and reported as AEs as they will be collected and analysed separately. However, abnormal laboratory findings or other objective measurements that meet the criteria for a SAE, result in discontinuation of the study medication, require medical intervention or are judged by the investigator to be clinically significant changes from baseline values should be captured and reported on the AE pages of the e-CRF and reported as an SAE.

When recording an abnormal laboratory finding on the AE pages of the e-CRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if this is available (for example, “anaemia” rather than “decreased red blood cell count” or “haemoglobin = 10.5 g/dl”).

### 9.2.3 Baseline Medical Conditions

Medical conditions present at baseline that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are NOT to be considered AEs. These medical conditions should be adequately documented on the medical history page of the e-CRF. However, baseline medical conditions, other than the disease under study, that worsen in severity or frequency during the study should be recorded and reported as AEs.

### 9.2.4 Worsening of Knee Osteoarthritis

In this protocol, symptoms and signs of worsening of OA will usually be considered in the context of efficacy assessment, and recorded on “efficacy” pages of the e-CRF. Therefore, symptoms of worsening of OA will not be considered as AEs nor recorded on the AE page of the e-CRF unless the event is considered possibly or probably related to the study medication (i.e., worsening is not consistent with the anticipated natural progression of the disease).

### 9.2.5 Eliciting Reports of Adverse Events

Adverse event data will be obtained by the investigator and/or his/her delegates at scheduled or unscheduled study visits, based on information spontaneously provided by the patient and/or through questioning of the patient. AE data thus collected must be reviewed and medically assessed before transcription into the e-CRF.

If a patient is seen by a physician not involved in the study in relation to an AE, the investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary for appropriate reporting of the event.

### 9.2.6 Recording Adverse Events

All AEs either observed by the investigator or reported by the patient (including the period between visits) will be recorded in the designated section of the e-CRF. Individual AEs will be evaluated by the investigator. This includes the dates of onset and resolution, intensity, outcome, action taken with study medication, evaluation of seriousness and causality between the study medication and/or concomitant therapy and the AE.

As the quality and precision of acquired AE data are critical, investigators should use the AE definitions provided in the above sections and should observe the following guidelines when completing the AE pages of the e-CRF:

- whenever possible, recognised medical terms should be used to describe AEs rather than colloquialisms (for example, "influenza" rather than "flu"), and abbreviations should be avoided;
- AEs should be described using a specific clinical diagnosis, if available, rather than a list of component signs or symptoms (for example, "congestive heart failure" rather than "dyspnoea, rales and cyanosis");
- however, signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual AEs:
- provisional diagnoses (e.g., "suspected myocardial infarction") are acceptable but should be followed up to a definite diagnosis when eventually available;

- AEs occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the e-CRF. The investigator should be invited to provide his/her opinion of which is the primary AE.

### 9.2.7 Reporting Adverse Events

Complete and appropriate data on all AEs experienced for the duration of the reporting period, as defined in Section 9.4, will be recorded on an ongoing basis in the AE pages of the e-CRF.

It is important that each AE report includes a description of the event, whether it is considered serious (according to Section 9.3.1), its duration (onset and resolution dates), its intensity, its relationship to the study medication, any other potential causality factors, any concomitant treatment given or other action taken (including dose modification or discontinuation of the study medication) and its outcome as of the end of the reporting period.

### 9.2.8 Evaluation of Intensity

The investigator will use the following definitions to code the intensity of the event:

- **mild**: usually transient, requiring no special treatment and does not interfere with the patient's daily activities;
- **moderate**: traditionally introduces a low level of inconvenience or concern to the patient and may interfere with daily activities, but is usually relieved by simple therapeutic measures;
- **severe**: causes an interruption of the patient's usual daily activity and traditionally requires systemic drug therapy or other treatment.

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily an SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs listed in Section 9.3.1.

### 9.2.9 Evaluation of Causality

Every effort should be made by the investigator to explain each AE and assess its causal relationship to the administration of the study medication. The relationship of the study medication to an AE, as causing or contributing to the AE, will be characterised as defined below:

- **unrelated**: evidence indicates no plausible direct relationship to the study medication;
- **unlikely**: suggests other conditions are likely to account for the event including concurrent illness, progression, or expression of the disease state, or reaction to concurrent medication;
- **possible**: suggests that the association of the event with the study medication is unknown; however, the AE is not reasonably supported by other conditions;
- **probable**: suggests that a reasonable temporal sequence of the event with medication administration exists and, based on the investigator's clinical experience, the association of the event with study medication seems likely;

- **certain**: follows anticipated response to study medication and is confirmed by discontinuing and/or rechallenge;
- **unknown/unassessable**.

The causality rating of AEs is usually determined during the examination by the investigator.

## 9.3 Serious Adverse Event

### 9.3.1 Definition of a Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

The term “life threatening” in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that may not be immediately life threatening or result in death or hospitalisation but could jeopardise the patient or require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation, or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

### 9.3.2 Reporting Serious Adverse Events by the Investigator

All AEs classified by the investigator as serious or new information on a previously reported SAE (irrespective of suspected cause), must be reported immediately. The investigator shall complete as fully as possible and **fax the SAE Report Form** with a copy of the clinical history (with patient identity protected) **immediately**, in any case no later than within 24 hours of discovery, to the fax number below. SAEs must also be recorded in the AE section of the e-CRF.

**Study Contact Information for Reporting Serious Adverse Events (SAEs):**

**PharmaLex GmbH**
Dr. Christiane Kreutzer (Manager Pharmacovigilance)
Bahnstrasse 42-46
D-61381 Friedrichsdorf
Germany

**Fax: +49 6172 995623**
E-mail: clinical-trial-TRB@pharmalex-group.com

Even if an SAE Report Form cannot be fully completed at this stage, the following minimum information is required as initial notification:

- (description) term and short description of SAE, date of occurrence;
- medical confirmation of the event;
- assessment of seriousness and causality, reason for considering the event serious;
- patient's identification details (patient trial number and at least one of the following: year of birth, age, sex);
- suspected investigational medicinal product;
- study medication administration details, e.g., date of first administration;
- identifiable reporter (date and signature of investigator);
- trial number, EudraCT number.

All SAEs must be documented and followed up until the event has either resolved, subsided, stabilised, disappeared, is otherwise explained or the study patient is lost to follow-up. All follow-up activities must be reported in a timely manner, on one or more consecutive SAE Report Forms. All fields with additional or changed information must be completed and the SAE Report Form should be forwarded to the Study Contact for Reporting Serious Adverse Events as soon as possible but at the latest within 24 hours for fatal or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) and 7 calendar days for all other SAEs after receipt of the new information. Clinically significant laboratory abnormalities will be followed up until they have returned to normal or a satisfactory explanation has been provided. Follow-up reports relative to the subsequent course of an AE noted for any patient must be submitted to the sponsor.

Serious adverse events occurring after completion of the study and which are justifiably considered to be related to the use of the study medication must also be reported.

The reference safety information used by the sponsor for the assessment of expectedness of an event will be the current Summary of Product Characteristics for Diacerein in Austria.

### 9.3.3 Study Specific Expedited Reporting Procedure(s)

The following events, while not considered SAEs, shall be reported as SAEs for monitoring and follow-up:

- overdose of study medication, drug dependency or abuse
- pregnancy

If any of these events occur during the study, including during the SAE follow-up period after the study has ended, the event must be reported to the Study Contact for Reporting SAEs without delay. The SAE Report Form should be used to report the event, even though the event is not considered an SAE in itself. Pregnancies should be followed up until delivery, and the Study Contact for Reporting SAEs informed of the outcome.

### 9.3.4 Procedures to be Followed in the Event of Pregnancy

The risks of Diacerein treatment during pregnancy have not been evaluated. The minimum age at inclusion has been set at 50 years of age to avoid the chance of pregnancy. However, the patient must be instructed to discontinue study medication and inform the investigator immediately if she becomes pregnant during the study treatment period. The investigator should report all pregnancies to the Study Contact for Reporting SAEs within 24 hours of becoming aware of the pregnancy. The investigator should explain to the patient that she should inform the study site of the outcome of the pregnancy. The patient should also be counselled regarding the potential for recurrence of disease when treatment is stopped and the availability of alternative treatment options. Monitoring of the patient should continue until conclusion of the pregnancy. The outcome of the pregnancy should be reported to the Study Contact for Reporting SAEs using the Clinical Trial Pregnancy Report Form (Appendix III).

### 9.3.5 Reporting to the Ethics Committee

The Sponsor is responsible for reporting SUSARs to the national Competent Authorities and the Ethics Committees.

Investigators will regularly receive a line listing of all SUSARs in a blinded version accompanied by a summary of the evolving safety profile of the IMP.

The investigator must comply with any applicable local requirements specifically related to the reporting of SAEs, involving his/her patients. If requested by the local regulation, the sponsor will advise the participating investigators to proceed with the submission of SAEs/SUSARs to their local ethics committees.

Furthermore, and in accordance with ICH GCP guidelines, the sponsor will inform the investigator of findings that could adversely affect the safety of patients, impact the conduct of the trial, or alter the Ethics Committee's approval/favourable opinion to continue the trial. The sponsor will inform the national competent authorities and the Ethics Committee of safety issues which might alter the current benefit-risk assessment of the IMP.

## 9.4 Type and Duration of the Follow-up of Patients After Adverse Events

Any AE (i.e. a new event or an exacerbation of a pre-existing condition) with an onset date starting from the day of written informed consent should be recorded in the appropriate section of the e-CRF.

All AEs must be entered in the appropriate section of the e-CRF. Details of the AEs observed by the investigator or reported by the patient must be entered into the e-CRF as follows: nature of the event, date of onset, intensity, duration, measures taken, outcome and relationship to the study medication.

New protocol related AEs (caused by any intervention required by the protocol) and updates on AEs with an ongoing or unknown outcome must be recorded up to the last day of study (including the follow-up, off study medication period of the study). Beyond this reporting period, any new unsolicited SAE spontaneously reported to the sponsor by the investigator would however be collected and processed.

If a patient is documented as lost to follow-up, ongoing/unknown outcome AEs will not be followed up.

Ongoing or recurring AEs will be recorded on the AE Forms for each visit at which they are present.

All ongoing/unknown outcome AEs will be monitored at least up to the last study visit. A last batch of queries will be sent after the last study visit if ongoing/unknown outcomes of reported AEs are pending.

After the last batch of queries with all collected data has been fully processed, the e-CRFs and database will no longer be updated. Only SAEs and medically relevant ongoing/unknown outcome AEs will be followed up until resolution or stabilisation under the CRO's responsibility.

For screening-failure patients, new AEs and updates must be recorded in the e-CRF until the date the patient was determined to be a screening failure. Beyond that date, only SAEs and medically relevant AEs will be followed up by the CRO.

### 9.5 Management of Liver Test Abnormalities

In this study, the eligible population also includes patients with mild to moderate hepatic impairment. Liver function will be monitored at visits 3, 4, 5, 7, 9 and 10. Any laboratory results showing an increase in liver test values according to Table 9-1 should be repeated within 3 days for all four parameters: SGOT (AST), SGPT (ALT), alkaline phosphatase and total bilirubin.

All abnormal laboratory liver values will be managed according to guidelines detailed in Table 9-1.

**Table 9-1: Biochemistry test values triggering repeat testing for liver tests**

| **Serum biochemistries** | **Limits** |
|---|---|
| SGOT (AST) | > 3 x ULN for patients with normal baseline measure |
| SGPT (ALT) | > 2-fold increase above baseline value for patients with elevated baseline value |
| Alkaline Phosphatase | > 1.5 x ULN |
| Bilirubin | > 2 x ULN |

*Reference: US FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009.*

**Table 9-2 Management of liver test abnormalities**

Repeat testing of SGOT (AST), SGPT (ALT), alkaline phosphatase and total bilirubin as soon as possible or within 3 calendar days.

| | |
|---|---|
| Monitoring | ▪ If the repeat value is unchanged or indicates decreasing activity, monitoring should continue at weekly intervals until the results return to baseline values.<br>▪ If any value has increased further, immediate close observation is |

| | |
|---|---|
| | required. Close observation includes:<br>Repeat liver enzyme and serum bilirubin tests once a week. The patient should be followed as clinically indicated until the event resolves to baseline or is otherwise explained, whichever comes first.<br>Study drug may be continued for a laboratory abnormality considered unrelated to study drug.<br>▪ Discontinue study drug if close monitoring is not possible. |
| Discontinuation | Permanently discontinue study drug and manage according to local medical practice (also refer to Section "Patient withdrawal criteria") if:<br>▪ SGPT or SGOT > 8 x ULN<br>▪ SGPT or SGOT > 5 x ULN for more than 2 weeks<br>▪ SGPT or SGOT > 3 x ULN and bilirubin > 2 x ULN<br>▪ SGPT or SGOT > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%). |

### 9.6 Data and Safety Monitoring Board

Each patient must be subjected to attentive AE monitoring. The degree of gravity, intensity and the relationship between the AE and the use of the studied product must be evaluated.

An independent Data and Safety Monitoring Board (DSMB) will be established prior to study enrollment. All members will be independent from the Sponsor and the participating investigators. The DSMB will monitor patient safety information and review the progress of the clinical study. The DSMB will make recommendations regarding the continuation, suspension or termination of this clinical study.

The following will be evaluated by DSMB to determine if the study is suspended or terminated:

- Occurrence of unanticipated AEs
- Occurrence of SAEs as defined in the protocol
- Benefits versus risks of the study

The DSMB will include a panel of experts recruited from outside of the institutions involved in this study. The DSMB will meet annually during the course of the study.

At periodic intervals, the CRO will complete a list of (S)AEs. The list will be given to the DSMB Chairperson. The DSMB Chairperson will convene a subsequent meeting with all the members of the DSMB.

## 10 STATISTICS

### 10.1 Sample Size Calculation

The sample size calculation has been established to test the non-inferiority of Diacerein vs. Celecoxib in the assessment of the change from baseline (Visit 2) in WOMAC pain subscale score at D182.

Assuming that:

- the mean decrease in WOMAC Pain score at D182 in the Diacerein treatment group will be the same as in the Celecoxib treatment group;
- a common standard deviation of 26 in the two treatment groups;
- a type I error set to α = 0.025 (one-sided condition) and (1-beta) power equal to 90%;
- and using PROC POWER in SAS® Version 9.2, the estimation provided for the one-sided, two sample t-test with equal allocation to two groups, 144 patients per treatment group is deemed to have adequate power to claim non-inferiority with a margin of 10 units. To allow for approximately 25% drop out, 200 patients will be recruited per treatment group, i.e., 400 patients in total.

## 10.2 Efficacy Endpoints

Statistical analyses during the course of this study will include:

- An analysis at 6 months (symptom study) when all patients assigned to the study treatment groups have completed their D182 visit or have been prematurely withdrawn from the study. The analysis will include data until Month 6 for the evaluation of the primary endpoint, exploratory symptoms and signs endpoints and safety endpoints.

- An exploratory analysis at 24 months (MRI structural study) for all safety, structural OA endpoints and symptoms and signs endpoints will be performed at the end of the study, i.e., when all patients included in the structural part of the study have completed their D728 study visit or have been prematurely withdrawn from the study.

### 10.2.1 Primary Efficacy Endpoint

The primary efficacy variable is the change from baseline (Visit 2) in WOMAC Pain subscale score after 182 days of treatment. An improvement is measured by a decrease in the mean WOMAC Pain score.

### 10.2.2 Exploratory Efficacy Endpoint

The exploratory efficacy variables are listed below for OA structural changes and for Symptoms and Signs of OA.

10.2.2.1 Exploratory Efficacy Endpoints for OA Structural Changes

- Cartilage volume loss from baseline (Visit 2) at D728 in the global knee and in the medial and the lateral compartments as evaluated by MRI will be computed by considering the relative percent change of each cartilage volume from baseline at D728. The cartilage volume loss will be expressed as a percentage.
- Change from baseline (Visit 2) at D728 in BML score as evaluated by MRI.
- Change from baseline (Visit 2) at D728 in synovitis (synovial membrane thickness) as evaluated by MRI.

10.2.2.2 Exploratory Efficacy Endpoints for Signs and Symptoms of OA

- Change from baseline (Visit 2) in WOMAC Pain subscale score at D728.
- Change from baseline (Visit 2) in WOMAC Stiffness and WOMAC Function subscale scores at D182 and D728.
- Change from baseline (Visit 2) in visual analogic pain scale (VAS - Huskisson's) at D182 and D728.

- Percentage of OARSI (Osteoarthritis Research Society International) responders at D182 and D728.

  Responders are defined based on the OMERACT-OARSI set of responder criteria [28] as follows:

  1. Relative change (percentage change) from baseline in WOMAC pain score or in WOMAC function score ≥ 50% and absolute change from baseline in WOMAC pain score or in WOMAC function score ≥ 20.

  or,

  2. If at least 2 out of 3 criteria met:
     - Relative change in WOMAC pain score ≥ 20% and absolute change in WOMAC pain score ≥ 10.
     - Relative change in WOMAC function score ≥ 20% and absolute change in WOMAC function score ≥ 10.
     - Relative change in Patient's global assessment of disease activity ≥ 20% and absolute change Patient's global assessment of disease activity ≥ 10.
- Percentage of patients with joint swelling and effusion at D182 and D728.
- Percentage of patients consuming rescue medication at D182 and D728.
- Change from baseline (Visit 2) in Patient's global assessment of disease activity at D182 and D728.
- Change from baseline (Visit 2) in Investigator's global assessment of disease activity at D182 and D728.
- Patient's global assessment of response to therapy at D182 and D728.
- Investigator's global assessment of response to therapy at D182 and D728.
- Change from baseline in (Visit 2) in Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from the SF-36 at D182 and D728.

### 10.3 Safety Variables

The safety outcomes will include the following items:

- Vital signs (blood pressure);
- Laboratory parameters;
- Physical examination;
- Adverse events;
- Concomitant medications;
- Compliance with the study product.
-

### 10.4 Analysis Population

Due to the design of the study - the primary analysis being conducted at 6 months on the 400 included patients in the symptoms part of the study; the 24 months analysis being conducted on approximately 100 patients participating to the structural study - two sets of Analyses populations will be defined: one for the analyses at 6 months, including the primary analysis, and one for the analyses at 24 months.

#### 10.4.1 Analysis Population for the Analysis at 6 Months (Primary Efficacy Endpoint)

- The Safety (SAF) population will be composed of all patients who took at least one dose of the study medication. Analyses on the SAF will be performed according to the product actually received.
- The Intent-to-Treat (ITT) population will be composed of all randomised patients who received at least one dose of the study medication, had an efficacy measurement at inclusion and at least one corresponding post-inclusion efficacy measurement (for the primary efficacy variable).
- Analyses on the ITT population will be performed according to the randomisation group regardless of the study medication actually received.
- The Per-Protocol (PP) population will be a subset of the ITT population and will include all patients who did not present any major violation of the protocol over the 6-month follow-up period.

#### 10.4.2 Analysis Population for the Analysis at 24 Months (Structural Study)

Due to the exploratory nature of the analyses, only one population will be considered. This population will be composed of all patients randomized and treated, and being selected for the 24 months structural study.

Reasons for exclusion from the PP population will be further described in the Statistical Analysis Plan (SAP).

#### 10.4.3 Populations Used for Each Statistical Analyses

The primary analysis of the primary endpoint (Month 6) will be based on the PP population. The primary efficacy analysis will be also performed using the ITT population to test the robustness of the results. Other efficacy analysis at month 6, unless otherwise specified, will be based on the ITT population. Safety analysis will be based on the SAF population.

The population for exploratory efficacy analyses at Month 24 will be based on the treatment at randomisation. Safety analyses population will be based on the actual treatment received.

## 10.5 Statistical Considerations

The primary analysis of the primary criterion is detailed in Section 10.7.3. All other efficacy and safety statistical results will be exploratory. No adjustment to control the type I error for multiplicity will be performed. For all other analyses than primary, statistical tests will be two-sided at 5% significance level. Statistical significance will be declared if the rounded p-value will be less than 5%.

The descriptive summary statistics will be provided according to the nature of the variables:

- Quantitative variable: number of observed values, mean and standard deviation, median, 95% Confidence Interval, first and third quartiles, minimum and maximum.
- Qualitative variable: number of observed values, number and percentage of patients by category.

Statistical analyses will be performed using SAS® software version 9.2 (SAS Institute, Cary, NC, USA).

A SAP describing the two analyses (at 6 months and 24 months, see Section 4.1) will be written during the study and finalised before primary analysis. These specifications will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

All study data will be at least presented in individual patient listing.

## 10.6 Handling of Drop-out and Missing Data

The detailed procedure will be included in the SAP and in the Final Report. The handling of missing data will follow the principles specified in the ICHE9 [29] and the CPMP/EWP/1776/99 Points to Consider on Missing Data guidelines [30].

No formal imputations will be performed for any of the variables and the analyses will be based on the Available Data Only approach, with the only exception being the main variable (WOMAC pain subscale) where missing data will be dropout due to safety problem or lack of efficacy.

The remaining continuous efficacy variables will not be imputed since the predefined approach Mixed Models for Repeated Measurements [31-32] is robust to the presence of missing at random (MAR) and conducts the analysis with all subjects despite the presence of missing data.

## 10.7 Statistical Analysis

### 10.7.1 Disposition of Patients

Disposition of patients, for both analyses (Month 6 and Month 24), will be described on all patients included and having signed an informed consent, for the two analyses. Description will be performed by treatment group (and globally) including randomised patients, patients who received at least once the study treatment, patients who completed the study, patients who discontinued from the study along with the reasons for discontinuation.

Protocol deviations including patients with at least one major deviation overall and by main category of deviation, patients with at least one minor deviation overall and by main category of minor deviation will be described by treatment group and globally.

### 10.7.2 Demography and Other Baseline Characteristics

Descriptive statistics will be presented for the two analyses for all collected data by treatment group and globally (Screening Visit or Inclusion Visit). The analysis will be performed on the ITT population for the 6 months analysis and on the ITT for the 24 months analysis.

For both analyses, the main characteristics of patients could also be described on the PP population if more than 15% of patients from the ITT population are excluded from the PP population.

No inferential analysis will be performed for the baseline comparability. Statistical tests will only be performed if any clinically significant unbalance between treatment groups appears to be of major importance for the interpretation of the primary efficacy criterion results.

Medical and surgical histories will be tabulated descriptively, presenting past and active medical conditions by pre-defined e-CRF body system, by treatment group and globally.

### 10.7.3 Primary Efficacy Analysis

The primary analysis of the primary efficacy variable will be based on the PP population.

Non-inferiority of Diacerein versus Celecoxib will be assessed by computing the difference in the mean change from baseline (Visit 2) in WOMAC Pain subscale score after 182 days of treatment between Diacerein and Celecoxib treatment groups.

The statistical hypotheses are the following:

- H0 (null hypothesis): the difference in the mean change from baseline at D182 between Diacerein and Celecoxib is superior or equal to 10 (non-inferiority margin),
- H1 (alternative one-sided hypothesis): the difference in the mean change from baseline at D182 between Diacerein and Celecoxib is inferior to 10 (non-inferiority margin) (on a scale of 0-100).

For non-inferiority claim, Diacerein will be proven to be non-inferior to Celecoxib if the upper bound of the 95% CI of the difference in the mean change from baseline at D182 between Diacerein and Celecoxib is inferior to10 (on a scale of 0 -100).

The primary analysis will be repeated on the ITT population to test robustness of the results. In the same way, Diacerein will be proven to be non-inferior to Celecoxib if the upper bound of the 95% CI of the difference in the mean change from baseline at D182 between Diacerein and Celecoxib is inferior to 10 (on a scale of 0-100).

A p-value for the non-inferiority testing between the two treatment groups will obtained using a one-sided Student t-test.

<u>Additional analysis of the primary efficacy criterion</u>

The primary analysis of the difference in the change from baseline in WOMAC Pain subscale score after 182 days between Diacerein and Celecoxib treatment groups will be complemented

using an Analysis of Covariance model (ANCOVA) at D182, with the treatment group as fixed factor and the WOMAC Pain subscale score value at baseline as a covariate.
The effects of the factor(s) centre and/or country, depending of the number of patients, could also be assessed in separate models.

### 10.7.4 Exploratory Efficacy Analysis

10.7.4.1 Exploratory Efficacy Analyses at 6 months (Day 182)

Exploratory efficacy analyses at 6 months concern signs and symptoms of OA only. Analyses will be performed on the ITT population.

Values at baseline and at each post-baseline visit will be summarised by treatment group. The change from baseline to each post-baseline visit will also be tabulated.

The difference in mean change from baseline between Diacerein and Celecoxib treatment groups will be tested, for exploratory purposes, with a Student t-test (Gaussian variable) or a Mann-Whitney test (non-Gaussian variable). Likewise, the comparison between Diacerein and Celecoxib treatment groups will be analysed with either a Chi-square or a Fisher exact test for qualitative data.

10.7.4.2 Exploratory Efficacy Analyses at 24 months (Day 728)

For all exploratory efficacy variables for OA Structural Changes and Signs and Symptoms at 24 months, analyses will be performed on the treatment at randomization population consistently with the analyses at Month 6, i.e., values at baseline and at each post-baseline visit, as well as the change from baseline to each post baseline visit will be summarised by treatment group. The same statistical tests as for the analysis at month 6 will be used.

Additional exploratory analyses could be performed by means of multivariate analyses, if relevant, and will be fully described in the SAP.

### 10.7.5 Compliance With the Study Product

Compliance with the study product will be described by treatment group for the two analyses (6 months and 24 months). No statistical test will be performed.

### 10.7.6 Safety Analysis

Safety data will be described by treatment group as detailed below. Description will be based on the SAF population for the analysis at 6 months and on the actual treatment received population for the analysis at 24 months.

10.7.6.1 Extent of Exposure

The duration of study participation (days) as well as the duration of treatment intake (days) will be tabulated by treatment group.

10.7.6.2 Adverse Events

An overall summary of adverse events will be presented by treatment group. Adverse events (incidence, relationship to the study medication) will be summarised by presenting the number and percentage of patients having any adverse event, having any event by body system and

having each individual adverse event. Adverse events that result in death, discontinuation or are serious will be presented separately:

- any other information, e.g. start and end date, intensity of adverse events or relatedness to study medication will be listed for all patients;
- patients who prematurely withdraw from the study will be displayed and summarised by primary reason and treatment.

Any AE reported throughout the study for a given patient will be classified by preferred term and corresponding System Organ Class, using the most available version of the MedDRA terminology, prior to the database lock.

Number and percentage of patients reporting at least one event, presented by primary system organ class and/or preferred term will be provided by treatment group, for serious adverse events, emergent adverse event, SAEs, AEs related to the study treatment and AEs leading to permanent study discontinuation.

All SAEs and AEs leading to permanent study discontinuation will be listed and exhaustively described on an individual basis, by treatment group, including all reported information on the AEs e-CRF, as well as their onset date, duration and outcome.

#### 10.7.6.3 Laboratory Parameters

Laboratory tests: all laboratory results which are not within the laboratory normal ranges will be summarised in shift tables using normal ranges, in summary statistics of raw data and changes from screening values (mean, median, standard deviation, range) and by flagging of noteworthy values in data listings.

#### 10.7.6.4 Physical Examination

The number and percentages of patients with abnormal physical examinations will be summarised by treatment group, at each visit globally and by pre-defined body system. Appropriate listings will be generated for all the abnormal observations.

#### 10.7.6.5 Concomitant Medication

Concomitant treatments will be tabulated descriptively by treatment group using the WHO Drug dictionary and the ATC classification. Rescue therapy with acetaminophen and other authorised analgesics will be tabulated separately.

# 11 DATA HANDLING AND QUALITY ASSURANCE

## 11.1 Patient Identification, Enrolment, and Screening Logs

The investigator agrees to complete patient identification and screening/enrolment logs to permit easy identification of each patient during and after the study. These documents will be reviewed for completeness by the study monitor.

The patient identification log will be treated as confidential and will be filed by the investigator in the study file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patient by patient identification and date of birth. In cases where the patient is not randomised into the study, the date seen and date of birth will be used.

The investigator must also complete a patient screening/enrolment log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

### 11.2 Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the electronic Case Report Form (e-CRF): patient identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a patient should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by patient interview or other protocol required assessment (e.g., physical examination, laboratory assessment) and documented in the source documents.

### 11.3 Case Report Form Completion

Case report forms are provided for each patient in an electronic format.

Electronic Data Capture (eDC) will be used for this study.

The e-CRF will be developed by Inferential/Euraxi Pharma.

The study data will be transcribed by study-site personnel from the source documents onto an e-CRF, and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between the Sponsor and the study site. The electronic file will be considered to be the e-CRF.

Worksheets may be used for the capture of some data to facilitate completion of the e-CRF. Any such worksheets will become part of the patient's source documentation. All data relating to the study must be recorded in e-CRFs. Data must be entered into e-CRFs in English. Study site personnel must complete the e-CRF as soon as possible after a patient visit (to a maximum of 5 open days), and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (e.g., pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the e-CRFs are accurate and correct.

All e-CRF entries, corrections, and alterations must be made by the investigator or other authorised study-site personnel. If necessary, queries will be generated in the eDC tool.

If corrections to an e-CRF are needed after the initial entry into the e-CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.

- Clinical data manager can generate a query for resolution by the study-site personnel.

The completed e-CRFs must be reviewed and signed by the investigator named in the study protocol or by a designated co-investigator.

### 11.4 Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by Sponsor representatives. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for e-CRF completion will be provided and reviewed with study-site personnel before the start of the study. The study monitor will review e-CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

All procedures for the handling of data will be described in the Data Management Plan (DMP) developed by Inferential/Euraxi Pharma.

### 11.5 Monitoring/Audit

Representatives working on behalf of the Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data entered into the e-CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the e-CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the e-CRF are consistent with the original source data. Findings from this review of e-CRFs and source documents will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

Additionally, study-sites can be audited by representatives of the Sponsor (TRB Chemedica International SA), ArthroLab Inc., government regulatory authorities (e.g., Health Canada and other foreign regulatory agencies), to ensure that the study is being conducted in conformity with the protocol of the study, Good Clinical Practice and other regulatory aspects.

### 11.6 Archival of Data

At the end of the study, the investigator will be provided with a copy of each participant's data on a CD-ROM support. These data include the completed e-CRF, all e-CRF comments, history of all queries, all signature history and the full audit trail reports. These copies will be archived by

the centre for at least 15 years. This duration can be longer in some countries according to local regulation.

# 12 ETHICS

This study will be conducted in accordance with the final signed study protocol and according to current ICH GCP guidelines, the ethical principles that have their origins in the Declaration of Helsinki, last updated in Fortaleza, Brazil, October 2013, and with all applicable regulatory requirements of the individual countries where the study will take place.

## 12.1 Confidentiality

In order to maintain patient confidentiality, only a site number and patient number will identify all study patients on e-CRFs and other documentation submitted to the Sponsor.

## 12.2 Ethics Committee

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating centre or central IRB/IEC prior to study initiation. A copy of the approval must be sent to the Sponsor or designee before the study can start. The Investigator will obtain assurance of IRB/IEC compliance with local regulations. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study.

The IRB/IECs unconditional approval statement will be transmitted by the Investigator or the CRO to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB/IEC; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

## 12.3 Protocol Amendments

No modifications can be made to the protocol by the Investigator without prior discussion with, and authorisation by, the Sponsor.

The modification, presented as an amendment in written form to the protocol, will be signed by the different parties and submitted to the regulatory agencies which approved the protocol and the IRB/IEC.

Following approval, the amendment will be sent to all participating Investigators. The amendment cannot be acted upon prior to the outcome of this decision.

An amendment regarding minor modifications (administrative modifications) will be submitted to the regulatory agency for information purposes only.

### 12.4 Informed Consent

Prior to their participation in the study, patients will receive a complete and most recent IRB/IEC approved version of the patient's information (in easily comprehensible terms and in the local language) forms, the *MRI Consent Form* and an *Informed Consent Form*. Two different Consent Forms will be available; one for patients completing the 6-month study (primary outcome) and one for those completing the 24-month study. The *MRI Consent Form* will be available only to the patients completing the 24-month study. The objectives, methods and duration of participation, the main limitations of the protocol, and the possible risks and benefits of treatment will be explained in details to each potential patient. The patient is reminded that he/she can refuse to take part in this study and can, at any time and without personal prejudice, withdraw his/her consent.

The *MRI Consent Form* and the *Informed Consent Forms* will be submitted with the protocol to the IRB/IEC for approval.

### 12.5 Protocol Violations and Deviations

A protocol violation occurs when the patient or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety and primary endpoint criteria.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a patient.

Protocol violations and deviations will be documented in the monitoring visit report by the clinical monitor. The investigators will be notified of violations and deviations in writing by the monitor, and will report violations and deviations to the Sponsor or its designee. The IRB/IEC should be notified of protocol violations and substantial deviations that impact on the safety of the patients and integrity of the study in a timely manner. Other deviations from the protocol will be reported to the IRB/IEC according to local requirements.

All deviations from the study protocol and its amendments (if any) will be reported to the Sponsor via the monitoring report. Substantial deviations will be reported to the Sponsor by the CRO's project manager directly.

### 12.6 Study Reporting Requirements

The results of the study will be presented in clinical study reports at 6 months (Symptom study) and at 24 months (MRI structural study).

### 12.7 Publications

The results of the study could be presented or published by the Lead Principal Investigator in collaboration with the Sponsor's personnel involved in the study.

The results of this study cannot be published by the Lead Principal Investigator without prior agreement of the Sponsor.

The representatives of ArthroLab Inc. will verify the manuscripts prior to any public presentation in order to prevent premature publication of confidential results and to guarantee the patient rights of certain information that requires protection.

The Sponsor commits to return any manuscript which will be submitted to him for review/comments, within sixty days after receipt of said manuscript.

The Lead Investigator and the Sponsor will assume joint responsibility for the procedure related to the publication of the manuscript.

### 12.8 Financial Disclosure and Obligations

The Sponsor is insured under a liability insurance program subscribed by the Sponsor to cover its liability as Sponsor of clinical studies on a worldwide basis.

All relevant insurance documentation is included in the file submitted to any authorities approval of which is required. Each participating investigator receives the statement on insurance policy applicable in his / her country for filing in the investigator's study file

Details of financial arrangements and insurance are provided separately.

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## APPENDIX I: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

### Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

### General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic

interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

## Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

## Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

## Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

## Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, **where appropriate, made publicly available.**

## APPENDIX II: SERIOUS ADVERSE EVENTS FORM

**TRB Chemedica International SA**
**DAR-INT-14-01**
Serious Adverse Event Report Form PharmaLex
Attn. Pharmacovigilance Unit
**FAX No.: +49 (0) 6172-995623**
E-Mail: clinical-trial-TRB@pharmalex-group.com

| *For company use only:* | |
|---|---|
| *PLX-Case-ID:* | *Date received at PLX by:*<br>*(DD / MM / YYYY) / Signature* |
| *Comments:* | |

| Type of report : | Initial report ☐ | Follow up report ☐ |
|---|---|---|

| **1. Study Centre** | |
|---|---|
| Study Center No. | Country: |
| Principal Investigator: | Reporter's Name: |
| Date of this report: | Reporter's Signature: |

| **2. Patient demographics** | | | | |
|---|---|---|---|---|
| Patient Selection Number | Year of Birth | Sex | Height (cm) | Weight (kg) |
| | YYYY | M ☐ F ☐ | | |

| **3. Adverse event** *(to report additional events, please copy this page)* | |
|---|---|
| **Event Term***(group symptoms as a single disease, to be consistent with CRF)* | Onset date (DD / MM / YYYY) |
| | |
| **Description of event** *(course of AE including related signs/symptoms, relevant findings, countermeasures, confounding factors and suspected cause of the SAE)* | |

| 4. Seriousness | |
|---|---|
| ☐ Fatal | ☐ Disabling / Incapacitating |
| ☐ Life threatening | ☐ Congenital Anomaly |
| ☐ Required/prolonged hospitalisation | ☐ Important medical event |

| 5. Phase of study at the time of event | | |
|---|---|---|
| ☐ Screening | ☐ Treatment | |
| ☐ Wash-Out | ☐ Follow Up | |
| ☐ Other, please specify | | |
| **STUDY NAME/SPONSOR TRIAL NO.** | **STUDY CENTRE NO.** | **PATIENT NUMBER** |
| DAR-INT-14-01 | | |

| 6. Study drug information | | | | |
|---|---|---|---|---|
| **Study drug** | **Dose / unit** | **Frequency** | **First administration date** (DD / MM / YYYY) | **Last administration date** (DD / MM / YYYY) |
| | | | | |
| | | | | |

| 7. Action taken with suspect study drug | 8. Relationship to suspect study drug | 9. Severity of event | 10. Outcome of event *(at the time of this report)* |
|---|---|---|---|
| ☐ Dose unchanged<br>☐ Dose reduced<br>☐ Temporarily discontinued<br>☐ Permanently discontinued<br>☐ Not applicable<br>☐ Unknown | ☐ Certainly<br>☐ Probably<br>☐ Possibly<br>☐ Unlikely<br>☐ Unrelated<br>☐ Unassessable | ☐ Mild<br>☐ Moderate<br>☐ Severe | ☐ recovered date:_____<br>☐ recovering<br>☐ recovered with sequelae date:_____<br>☐ not recovered<br>☐ fatal date:_____<br>☐ unknown |

**Dechallenge:**
Did event abate after stopping study medication? ☐ Yes ☐ No ☐ N/A ☐ Unknown

**Rechallenge**
Did event reappear after reintroduction of study medication? ☐ Yes ☐ No ☐ N/A ☐ Unknown

**Unblinding**
Was blinding code broken? ☐ No ☐ Yes If yes, provide date: _____

**11. Concomitant medication** Yes ☐ No ☐ Suspect: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐
**TAKEN AT THE TIME OF SAE** *Exclude those to treat reaction, use attachment if necessary*

| | Medication/ Generic Name | Dose | Frequency | Route | Indication | Start Date DD / MM / YYYY | Stop Date DD / MM / YYYY |
|---|---|---|---|---|---|---|---|
| 1. | | | | | | | |
| 2. | | | | | | | |
| 3. | | | | | | | |
| 4. | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5. | | | | | | | |

**Suspect concomitant medication**: *If SAE is considered to be caused by one of the above-mentioned concomitant medications, please mark the corresponding check box in the table header.*

| **12. Relevant past medical history** *(e.g. allergies, hepatic/renal dysfunction)* Yes ☐ No ☐ | | | |
|---|---|---|---|
| | **Condition / Disease** | **Start Date** DD / MM / YYYY | **Stop Date** DD / MM / YYYY |
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |

| **13. Hospitalization Details** *(complete, if applicable)* | **12. Death Details** *(complete, if applicable)* |
|---|---|
| ☐ New hospitalization<br>☐ Prolongation of hospitalization<br>Admission date: _____<br>Discharge date: _____ | Date of death**:** _____<br>Primary cause(s) of death: _____<br>_____<br>Autopsy performed:☐ Yes ☐ No<br>*(if yes, please attach report)* |

| **STUDY NAME/SPONSOR TRIAL No.** | **STUDY CENTRE NO.** | **PATIENT NUMBER** |
|---|---|---|
| DAR-INT-14-01 | | |

| **14. Additional Information***(Continue on separate sheet, if needed)* |
|---|
| |

## APPENDIX III: CLINICAL TRIAL PREGNANCY REPORT FORM

**TRB Chemedica International SA**
**DAR-INT-14-01**
Pregnancy Report Form
PharmaLex
Attn. Pharmacovigilance Unit
**FAX No.: +49 (0) 6172-995623**
E-Mail: clinical-trial-TRB@pharmalex-group.com

| *For company use only:* | |
|---|---|
| *PLX-Case-ID:* | *Date received at PLX by:*<br><br>*(DD / MM / YYYY) / Signature* |
| *Comment:* | |

| Type of report : | Initial report ☐ | Follow up report ☐ |
|---|---|---|

| **1. Study Centre** | |
|---|---|
| Centre No. | Country: |
| Principal Investigator: | Reporter´s Name: |
| Date of this report: | Reporter's Signature: |

| **2. Patient demographics** | | | | |
|---|---|---|---|---|
| Patient Selection Number ( | Year of Birth | Sex | Height (cm) | Weight (Kg) |
| | YYYY | M ☐ F☐ | | |

| **3. Study medication** | | | | |
|---|---|---|---|---|
| Study drug | Dose / unit | Frequency | First administration date (DD / MM / YYYY) | Last administration date (DD / MM / YYYY) |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

| **4. Relevant maternal past medical history** *(including endocrinological problems, gynecological infections, infertility, menstrual disorders), use an additional page if required* | | | |
|---|---|---|---|
| | | Start Date DD / MM / YYYY | Stop Date DD / MM / YYYY |
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4 | | | |
| 5 | | | |
| 6. | | | |

Alcohol consumption No ☐ Yes ☐ since _____

Tobacco consumption No ☐ Yes ☐ since _____

**Previous pregnancies:**

Has mother been pregnant before? YES ☐ No ☐

No. of full term births: _____ No. of preterm births: _____

No. of miscarriages: _____ No. of elective abortions: _____

| STUDY NAME/SPONSOR TRIAL No. | STUDY CENTRE NO. | PATIENT NUMBER |
|---|---|---|
| DAR-INT-14-01 | | |

**5. Maternal medication history** *(including contraceptive methods used & recreational drugs) Use an additional page if required*

| | Medication/ Generic Name | Dose | Frequency | Route | Indication | Start Date DD / MM / YYYY | Stop Date DD / MM / YYYY |
|---|---|---|---|---|---|---|---|
| 1 | | | | | | | |
| 2 | | | | | | | |
| 3 | | | | | | | |
| 4 | | | | | | | |
| 5 | | | | | | | |
| 6 | | | | | | | |

**6. Relevant paternal past medical history** *(including cancer, urological diseases) Use an additional page if required*

| | Condition / Disease | Start Date DD / MM / YYYY | Stop Date DD / MM / YYYY |
|---|---|---|---|
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |

**7. Relevant paternal medication history** *Use an additional page if required*

| | Medication / Generic Name | Dose | Frequency | Route | Indication | Start Date DD / MM / YYYY | Stop Date DD / MM / YYYY |
|---|---|---|---|---|---|---|---|
| 1 | | | | | | | |
| 2 | | | | | | | |
| 3 | | | | | | | |
| 4 | | | | | | | |

**8. Pregnancy Information**

| | DD / MM / YYYY |
|---|---|
| Pregnancy diagnosis date: | |
| Presumed conception date: | |
| Last menstrual period date: | |

| Estimated delivery date: | |
|---|---|
| *Please indicate the reason for contraceptive failure:* | |

| STUDY NAME/SPONSOR TRIAL No. | STUDY CENTRE NO. | PATIENT NUMBER |
|---|---|---|
| DAR-INT-14-01 | | |

| **9. Pregnancy Follow up** |
|---|
| Has the patient already been referred to an Obstetrician / Gynaecologist? YES ☐ NO ☐ |
| If yes, please provide Obstetrician / Gynaecologist contact details |
| Description of Pregnancy *(e.g. abnormal findings, premature termination) Use an additional page if required:* |

**10. Outcome of Pregnancy**

☐ Full Term
☐ Premature Birth
☐ Spontaneous miscarriage (Date occurred: ____/____/____)
☐ Elective Termination:
Was the elective termination caused by any medical reason? YES ☐ NO
If Yes please provide details:

**11. Details of Birth**

☐ Healthy newborn
☐ Acquired diseases (e.g. infection, trauma, etc.), please specify_____
☐ Congenital anomaly/Birth Defect (please complete a SAE Form), please specify_____
☐ Still birth

APGAR Score: 1 min _____ 5 min _____ 10 min _____

Date of Birth: ____/____/____ SEX: M ☐ F☐

**12. Additional Information***(Continue on separate sheet, if needed)*

**APPENDIX IV: VISUAL ANALOGUEPAIN SCALE (VAS-HUSKINSON'S)**

# VISUAL ANALOGUE SCALE (VAS) FOR PATIENTS

Please indicate the amount of pain you have been feeling in the studied knee over the last 48 hours by placing a vertical mark «|» on the line below. To make your assessment, please take into consideration the pain you felt over the past 48 hours while walking.

No Pain _____ Extreme Pain Score_____

**APPENDIX V: WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0**

# WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

## INSTRUCTIONS FOR PATIENTS

In sections A, B and C, reply to the questions by placing a « | » on the horizontal line. See examples below:

1. If you place the « | » on the left end of the line, for example as follows:

|——————————————————————
No Extreme

This means that you are feeling no pain.

2. If you place the « | » on the right end of the line, for example as follows:

——————————————————————|
No Extreme

This means that you are feeling extreme pain.

3. Do not forget the following information:
   a) The more your « | » is on the right, the **more** pain you feel;
   b) The more your « | » is on the left, the **less** pain you feel;
   c) Do not place a « | » outside of the line.

You will be asked to indicate on this type of scale, the degree of pain, stiffness or incapacity felt in your _____ knee during the last 48 hours because of osteoarthritis. Please note that the more you place your « | » on the right, the more you feel pain, or stiffness and incapacity. Indicate the intensity of the pain, stiffness and incapacity you feel because of osteoarthritis in your studied knee

# WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

## SECTION A

Think of the pain you felt in your _____ knee because of osteoarthritis over the last 48 hours. (Please mark your answer by placing a «|» on the scale.

**QUESTION: What was the intensity of the pain you felt?**

1. When you walked on a flat surface?

No Extreme Score_____

2. When you walked up or down a flight of stairs?

No Extreme Score_____

3. When you were in bed at night?

No Extreme Score_____

4. When you were sitting or lying down?

No Extreme Score_____

5. When you were standing up?

No Extreme Score_____

## SECTION B

Think about the stiffness (but not about the pain) you felt in your _____ knee because of arthritis over the last 48 hours. Stiffness is a feeling of reduction in the facility to move your knee. (Please mark your answers by placing a «|» on the line).

6. What was the degree of stiffness you felt when you woke up in the morning?

No Extreme Score_____

7. What degree of stiffness did you feel during the course of the day, after having been sitting down, lying down, or resting?

No Extreme Score_____

# WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

## SECTION C

Think of the difficulty that you had during the last 48 hours because of osteoarthritis in your _____ knee while performing daily activities. This refers to your aptitude to move and take care of yourself. (Please mark your answers by placing a **«I»** on the line)

**QUESTION:** Over the last 48 hours, what was the degree of difficulty you experienced:

8. When you walked down a flight of stairs?

No _____ Extreme Score_____

9. When you walked up a flight of stairs?

No _____ Extreme Score_____

10. When you got up from a sitting position?

No _____ Extreme Score_____

11. When you were standing up?

No _____ Extreme Score_____

12. When you leaned towards the ground?

No _____ Extreme Score_____

13. When you walked on a flat surface?

No _____ Extreme Score_____

14. When you climbed into or got out of a car or a bus?

No _____ Extreme Score_____

15. When you went shopping?

No _____ Extreme Score_____

# WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

**QUESTION: What was the degree of difficulty you experienced:**

16. When you put your socks on?

No _____ Extreme Score_____

17. When you got out of bed?

No _____ Extreme Score_____

18. When you removed your socks?

No _____ Extreme Score_____

19. When you lay on the bed?

No _____ Extreme Score_____

20. When you got into or out of the bath?

No _____ Extreme Score_____

21. When you sat down?

No _____ Extreme Score_____

22. When you sat down on the toilet?

No _____ Extreme Score_____

23. When you carried out heavy domestic tasks?

No _____ Extreme Score_____

24. When you carried out small domestic tasks?

No _____ Extreme Score_____

Thank you for completing this questionnaire. Please add your initials and the date before giving the questionnaire to the Investigator/Study Nurse.

Initials:_____ Date:_____/_____/_____
DD MMM YYYY

## APPENDIX VI: SHORT-FORM 36 QUESTIONNAIRE

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

| Much better now than one year ago | Somewhat better now than one year ago | About the same as one year ago | Somewhat worse now than one year ago | Much worse now than one year ago |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports . . . . . | 1 | 2 | 3 |
| b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | 1 | 2 | 3 |
| c Lifting or carrying groceries . . . . . | 1 | 2 | 3 |
| d Climbing <u>several</u> flights of stairs . . . . . | 1 | 2 | 3 |
| e Climbing <u>one</u> flight of stairs . . . . . | 1 | 2 | 3 |
| f Bending, kneeling, or stooping . . . . . | 1 | 2 | 3 |
| g Walking <u>more than a kilometer</u> . . . . . | 1 | 2 | 3 |
| h Walking <u>several hundred meters</u> . . . . . | 1 | 2 | 3 |
| i Walking <u>one hundred meters</u> . . . . . | 1 | 2 | 3 |
| j Bathing or dressing yourself . . . . . | 1 | 2 | 3 |

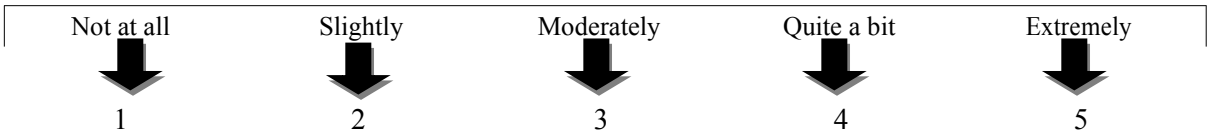
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Cut down on the amount of time you spent on work or other activities | 1 | 2 | 3 | 4 | 5 |
| b Accomplished less than you would like | 1 | 2 | 3 | 4 | 5 |
| c Were limited in the kind of work or other activities | 1 | 2 | 3 | 4 | 5 |
| d Had difficulty performing the work or other activities (for example, it took extra effort) | 1 | 2 | 3 | 4 | 5 |

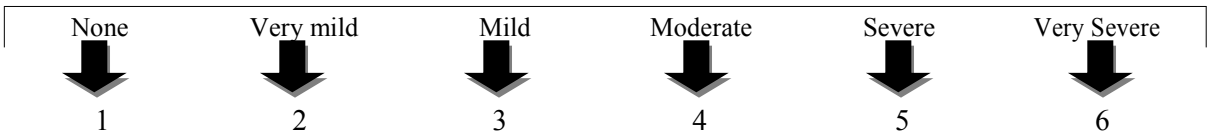
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Cut down on the amount of time you spent on work or other activities | 1 | 2 | 3 | 4 | 5 |
| b. Accomplished less than you would like | 1 | 2 | 3 | 4 | 5 |
| c. Did work or other activities less carefully than usual | 1 | 2 | 3 | 4 | 5 |

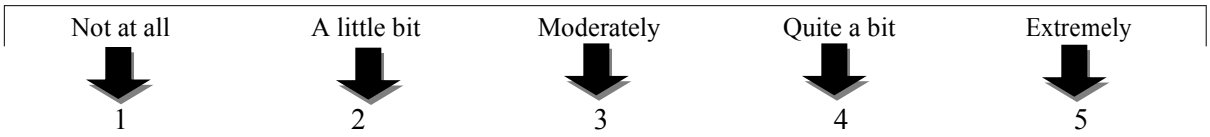
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?




7. How much bodily pain have you had during the past 4 weeks?




8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Did you feel full of life? . . . . . | 1 | 2 | 3 | 4 | 5 |
| b Have you been very nervous? . . . . . | 1 | 2 | 3 | 4 | 5 |
| c Have you felt so down in the dumps that nothing could cheer you up? . . . . . | 1 | 2 | 3 | 4 | 5 |
| d Have you felt calm and peaceful? . . . . . | 1 | 2 | 3 | 4 | 5 |
| e Did you have a lot of energy? . . . . . | 1 | 2 | 3 | 4 | 5 |
| f Have you felt downhearted and depressed? . . . . . | 1 | 2 | 3 | 4 | 5 |
| g Did you feel worn out? . . . . . | 1 | 2 | 3 | 4 | 5 |
| h Have you been happy? . . . . . | 1 | 2 | 3 | 4 | 5 |
| i Did you feel tired? . . . . . | 1 | 2 | 3 | 4 | 5 |

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a I seem to get sick a little easier than other people . . . . . | 1 | 2 | 3 | 4 | 5 |
| b I am as healthy as anybody I know . . . . . | 1 | 2 | 3 | 4 | 5 |
| c I expect my health to get worse . . . . . | 1 | 2 | 3 | 4 | 5 |
| d My health is excellent . . . . . | 1 | 2 | 3 | 4 | 5 |

Thank you for completing these questions!

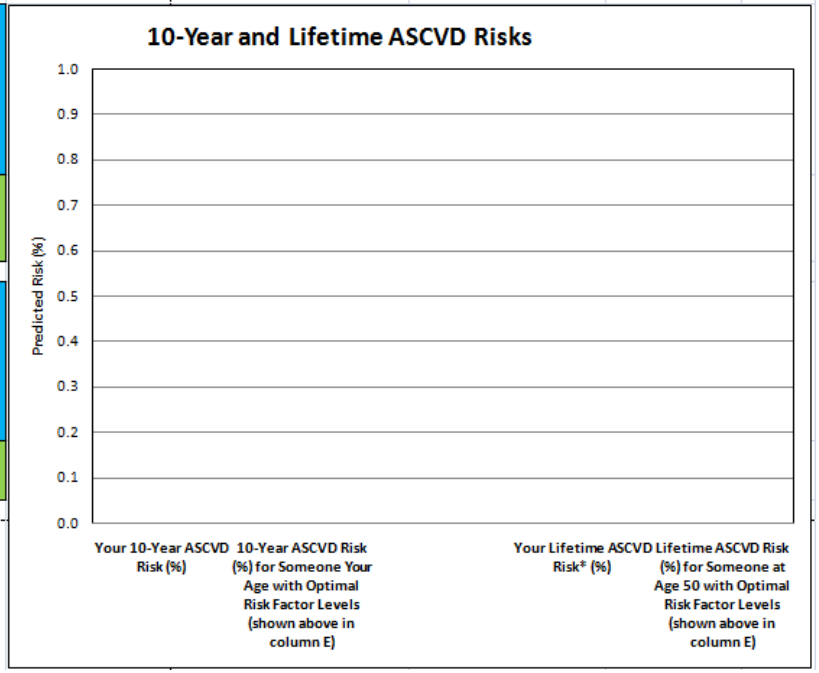
Initials : _____

Date : ___ / _____ / _____
DD / MMM / YYYY

## APPENDIX VII A: AHA CV GLOBAL RISK ASSESSMENT SCORING

Adapted from : American College of Cardiology (ACC) / American Heart Association(AHA) Assessment of Cardiovascular Risk (2013)

| | A | B | C | D | E | F | H |
|---|---|---|---|---|---|---|---|
| 1 | | | Enter patient values in this column | | | | |
| 2 | **Risk Factor** | **Units** | **Value** | Acceptable range of values | Optimal values | | |
| 3 | **Sex** | M (for males) or F (for females) | | M or F | | | |
| 4 | **Age** | years | | 20-79 | | | |
| 5 | **Race** | AA (for African Americans) or WH (for whites or others) | | AA or WH | | | |
| 6 | **Total Cholesterol** | mg/dL | | 130-320 | 170 | | |
| 7 | **HDL-Cholesterol** | mg/dL | | 20-100 | 50 | | |
| 8 | **Systolic Blood Pressure** | mm Hg | | 90-200 | 110 | | |
| 9 | **Treatment for High Blood Pressure** | Y (for yes) or N (for no) | | Y or N | N | | |
| 10 | **Diabetes** | Y (for yes) or N (for no) | | Y or N | N | | |
| 11 | **Smoker** | Y (for yes) or N (for no) | | Y or N | N | | |
| 12 | | | | | | | |
| 13 | **Your 10-Year ASCVD Risk (%)** | **This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter M or F for Gender Enter WH or AA for race Enter 130-320 for TC value Enter 20-100 for HDL value Enter 90-200 for SBP value Enter Y or N for treatment for hypertension Enter Y or N for Diabetes Enter Y or N for Smoker** | | | | | |
| 14 | 10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E) | **Enter M or F for Gender This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter WH or AA for race** | | | | | |
| 15 | | | | | | | |
| 16 | **Your Lifetime ASCVD Risk* (%)** | **This calculator only provides lifetime risk estimates for individuals 20 to 59 years of age Enter M or F for Gender Enter 130-320 for TC value Enter 90-200 for SBP value Enter Y or N for treatment for Hypertension Enter Y or N for Diabetes Enter Y or N for Smoker** | | | | | |
| 17 | Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E) | **Enter M or F for gender** | | | | | |
| 18 | | | | | | | |
| | ***This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches. While 10-year risk estimates are derived from** | | | | | | |



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 19 | **methods and data using continuous variables, the reported estimate of lifetime risk is based on assigning each person into one of 5 mutually exclusive sex-specific groups, as per Lloyd-Jones et al., Circulation 2006; 113(6):791-8. Within each of the 5 groups, each person receives the same lifetime risk estimate. In other words, using this approach, there are only 5 possible lifetime risk estimates reported for men and only 5 possible lifetime risk estimates reported for women. In some cases, the average risk for the group will underestimate the individual's true lifetime risk. This feature of lifetime risk estimation will result in the estimated lifetime risk being less than the estimated 10-year risk. In these cases, the 10-year risk should be the primary focus for the risk discussion and risk reduction efforts. As further data becomes available and incorporated and methods mature, lifetime risk estimates based on continuous variables will be possible.** | **For patients and the public: *This is the lifetime risk of cardiovascular diseases, including stroke, for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different mathematical approaches. If this is the case, the 10-year risk should be the primary focus for your risk discussion with your provider and for your efforts to reduce your risk.** | | | | | |
| 20 | | | | | | | |
| 21 | Abbreviations: AA = African American; ASCVD = Atherosclerotic cardiovascular disease, defined as CHD death, nonfatal myocardial infarction, or fatal or nonfatal stroke; F = Female; M = Male; N = No; WH = White; Y = Yes. | | | | | | |

## APPENDIX VII B: 10-YEAR ABSOLUTE RISK FOR TOTAL CVD ESTIMATED FROM FRAMINGHAM DATA

Adapted from d'Agostino RB et al., (2008) [33]

**10-Year CVD Risk (%)**

| Men | Women |
|---|---|
| <1 | <1 |
| 1.1 | <1 |
| 1.4 | 1.0 |
| 1.6 | 1.2 |
| 1.9 | 1.5 |
| 2.3 | 1.7 |
| 2.8 | 2.0 |
| 3.3 | 2.4 |
| 3.9 | 2.8 |
| 4.7 | 3.3 |
| 5.6 | 3.9 |
| 6.7 | 4.5 |
| 7.9 | 5.3 |
| 9.4 | 6.3 |
| 11.2 | 7.3 |
| 13.3 | 8.6 |
| 15.6 | 10.0 |
| 18.4 | 11.7 |
| 21.6 | 13.7 |
| 25.3 | 15.9 |
| 29.4 | 18.5 |
| >30 | 21.5 |
| >30 | 24.8 |
| >30 | 27.5 |
| >30 | >30 |

| |
|---|
| Low risk |
| Intermediate risk |
| High risk |

**APPENDIX VIII: PATIENT'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY**

## Patient's global assessment of disease activity

Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:

Very Well _____ Very poorly Score_____

**APPENDIX IX: INVESTIGATOR'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY**

## Investigator's global assessment of disease activity

Please, mark an X on the line below to indicate your assessment of your patient's disease activity (independent of the patient's self-assessment):

Very Good _____ Very Bad  Score_____

## APPENDIX X: PATIENT'S GLOBAL ASSESSMENT OF RESPONSE TO THERAPY

### Patient's global assessment of response to therapy

Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how your symptoms are now, compared with how they were before you began taking medication in this study*:*

Very Well _____ Very poorly Score_____

## APPENDIX XI: INVESTIGATOR'S GLOBAL ASSESSMENT OF RESPONSE TO THERAPY

### Investigator's global assessment of response to therapy

Please make a mark below to show how your patient's symptoms are now, compared with how they were before he/she began taking medication in this study (independent of the patient's self-assessment):

Very Good _____ Very Bad  Score_____