Anapharm Bioanalytics

[redacted]

# CLINICAL STUDY PROTOCOL

**Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions**

**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

**Short Title: BE Etoricoxib 120 mg FCT SD fasting**

## EMA Regulation

**Sponsor: PrJSC "Pharmaceutical firm "Darnitsa"**

**Version and Date: Final 01, 23.DEC.20**

## TABLE OF CONTENTS

## 1. STUDY SYNOPSIS

| | |
|---|---|
| **Title of Study** | Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions. |
| **Clinical Study Code** | 20ANE-3489C |
| **Sponsor Study Code** | ETR01-E |
| **Phase** | Phase I (Bioequivalence) |
| **Sponsor** | PrJSC "Pharmaceutical firm "Darnitsa", Ukraine |
| **Clinical Unit** | Erciyes University Hakan Cetinsaya GCP and Research Center, Turkey |
| **Global CRO** | Anapharm Europe, S.L.U., Spain |
| **Bioanalytical Laboratory** | Anapharm Europe, S.L.U., Spain |
| **Statistics Facility** | Medical Statistics Core Facility, IDIBAPS – Hospital Clinic Barcelona, Spain |
| **Study Medication** | **Test product (T):**<br>Name of the product: Exib<br>Pharmaceutical form: Film-coated tablets<br>Strength: 120 mg<br>Content:<br>- Active ingredient: etoricoxib<br>- Excipients: core - calcium hydrogen phosphate, microcrystalline cellulose (type 112), croscarmellose sodium, crosspovidone (XL-10), sodium stearyl fumarate, talc; tablet coating - opadray II 85F green 85F210083<br>Mode of administration: Oral use<br>Manufacturer (country): PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine)<br><br>**Reference product (R):**<br>Name of the product: Arcoxia<br>Pharmaceutical form: Film-coated tablets<br>Strength: 120 mg<br>Content:<br>- Active ingredient: etoricoxib<br>- Excipients: core - calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose; tablet coating - carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin, indigo carmine lake (E132), yellow ferric oxide (E172).<br>Mode of administration: Oral use<br>Manufacturer (country): Merck Sharp&Dohme B.V., The Netherlands<br>Country of purchase: Lithuania<br>MAH: UAB "Merck Sharp&Dohme", Lithuania |
| **Study Objectives** | Primary objective: To evaluate and compare the bioavailability (BA) and therefore to assess the bioequivalence (BE) between a Test formulation of Exib 120 mg film-coated tablets manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine) and a Reference formulation of Arcoxia® 120 mg film-coated tablets manufactured by Merck Sharp&Dohme B.V. (The Netherlands) when administered orally at the same dose level to 28 healthy volunteers under fasting conditions, in a 2-way crossover design. |

| | |
|---|---|
| | Secondary objective: To assess the safety and tolerability of both formulations. |
| **Study Design** | Open-label, two-period, two-sequence, two-way crossover, randomised, single dose bioequivalence study in healthy male volunteers under fasting conditions with a washout period of at least 14 days. |
| **Planned Subjects** | 28 subjects will be included in the study. |
| **Main Eligibility Criteria** | Healthy caucasian male volunteers, between 18 and 55 years (inclusively) with a Body Mass Index (BMI) within 18.5-30.0 kg/m$^2$, inclusively. |
| **Dosage and Route of Administration** | One film-coated tablet of either Test or Reference medication administered in the morning of Day 1 under at least 10 hours fasting conditions in each study period according to the study randomisation list.<br>Washout period of at least 14 days.<br>Oral administration with 240 mL of still water at ambient temperature. |
| **Pk Blood Sampling** | A total of 20 pk blood samples will be collected at the following timepoints in each study period: pre-dose and at 0.083, 0.167, 0.250, 0.333, 0.500, 0.750, 1.000, 1.250, 1.500, 2.000, 3.000, 4.000, 6.000, 8.000, 12.000, 24.000, 36.000, 48.000 and 72.000 hours post-dose. |
| **Primary Pk Parameters** | $C_{max}$ and $AUC_{0-72h}$*<br>*If there are concentrations below LLOQ (Lower Limit of Quantification) at 72 hours post-dose in at least one subject, then $AUC_{0-t}$ will be calculated for all volunteers instead of $AUC_{0-72h}$. |
| **Secondary Pk Parameters** | $t_{max}$<br>The following PK parameters will be calculated only in the event that not all subjects have quantifiable concentration levels at 72 hours post-dose (in addition to $AUC_{0-t}$, $C_{max}$ and $t_{max}$):<br>$AUC_{0-\infty}$, residual area, $k_{el}$ and $t_{1/2}$ |
| **Safety Parameters** | Adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiogram (ECG), physical examination, drugs of abuse, cotinine, alcohol test and COVID-19 real time (RT)-PCR Tests. |
| **Bioanalysis** | Etoricoxib will be determined in plasma using a validated bioanalytical Liquid Chromatography, tandem Mass Spectrometry (LC/MS/MS) method. |
| **Statistical Analysis** | Pharmacokinetic (pk): Pk parameters will be assessed using a non-compartmental approach with a log-linear terminal phase assumption.<br>$C_{max}$ and $AUC_{0-72h}$ (or $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, if applicable) will be statistically analysed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model will be the subject effect (nested within sequence), the treatment received, the period at which it was given, as well as the sequence in which each treatment is received.<br>The 90% Confidence Interval (CI) for the exponential of the difference in Least square means (LSmeans) between the Test and Reference products will be calculated for the ln-transformed $C_{max}$ and $AUC_{0-72h}$ (or $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, if applicable) parameters (Test to Reference ratio of geometric LSmeans).<br>Safety: Descriptive statistical analysis will be performed. |
| **Bioequivalence Assessment** | The ratio of geometric LSmeans with corresponding 90% CI calculated from the exponential of the difference between the Test and Reference products for the ln-transformed parameters $C_{max}$ and $AUC_{0-72h}$ (or $C_{max}$ and $AUC_{0-t}$, if applicable) should both be within the acceptance interval of 80.00 - 125.00%. |

## 2. LIST OF ABREVIATIONS AND DEFINITION OF TERMS

| TERM | DEFINITION |
|---|---|
| ADR | Adverse Reaction |
| AE | Adverse Event |
| ALT | Alanine transaminase |
| AMIS | Analytical Methodology Information Sheet |
| ANOVA | Analysis of Variance |
| ASA | Acetylsalicylic Acid |
| AST | Aspartate transaminase |
| AUC | Area under the Concentration-time Curve |
| $AUC_{0-\infty}$ | AUC from time zero to infinity |
| $AUC_{0-72h}$ | AUC from time zero to 72 hours |
| $AUC_{0-t}$ | AUC from time zero to the last quantifiable concentration |
| BA | Bioavailability |
| BE | Bioequivalence |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| COVID-19 | Coronavirus disease - 19 |
| COX-2 | Cyclo-oxygenase-2 |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CSM | Clinical Study Monitor |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTA | Clinical Trial Application |
| CU | Clinical Unit |
| CV | Coefficient of Variation |
| CYP | Cytochrome P450 |
| DBP | Diastolic Blood Pressure |
| ECG | Electrocardiogram |
| EE | Ethinyl estradiol |
| EMA | European Medicines Agency |
| ET | Early termination |
| EU | European Union |
| FCT | Film-coated tablets |
| FU | Follow up |
| GCP | Good Clinical Practice |

| | |
|---|---|
| GI | Gastro-intestinal |
| GLM | Generalised Linear Model |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HIV-Ab | Human immunodeficiency virus antibody |
| HR | Heart rate |
| HRT | Hormone Replacement Therapy |
| ICF | Informed Consent Form |
| ICH | International Conference of Harmonization |
| IEC | Independent Ethics Committee |
| IF | Investigator's File |
| IMP | Investigational Medicinal Product |
| INR | International Normalised Ratio (INR) |
| $K_{el}$ | Elimination rate constant |
| LC/MS/MS | Liquid Chromatography, tandem Mass Spectrometry |
| LLOQ | Lower Limit of Quantification |
| LSLV | Last Subject Last Visit |
| LSmeans | Least square means |
| MAH | Marketing Authorisation Holder |
| MEDAL | Multinational Etoricoxib and Diclofenac Arthritis Long-term |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| mmHg | Millimetres of mercury |
| NSAIDs | Nonsteroidal Anti-inflammatory Drugs |
| OA | Osteoarthritis |
| OTC | Over the counter |
| PI | Principal Investigator |
| Pk | Pharmacokinetics |
| POB | Bowel perforation, obstruction, or haemorrhage |
| PT | Preferred term |
| PUB | Perforations, ulcers and bleeds |
| QC | Quality Control |
| QPPV | Qualified Person for Pharmacovigilance |
| R | Reference product/medication |
| RA | Rheumatoid Arthritis |
| RT | Real Time |

| | |
|---|---|
| SAE | Serious Adverse Event |
| SAS® | Statistical Analysis System |
| SBP | Systolic blood pressure |
| SCR | Screening |
| SIS | Subject Information Sheet |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Event Reaction |
| T | Test product/medication |
| $t_{1/2}$ | Terminal elimination half-life |
| $t_{max}$ | Time at which the maximum plasma concentration occurs |
| TMF | Trial Master File |

## 3. PROTOCOL APPROVAL/SIGNATURE PAGES

**By PrJSC "Pharmaceutical firm "Darnitsa" (Sponsor)**

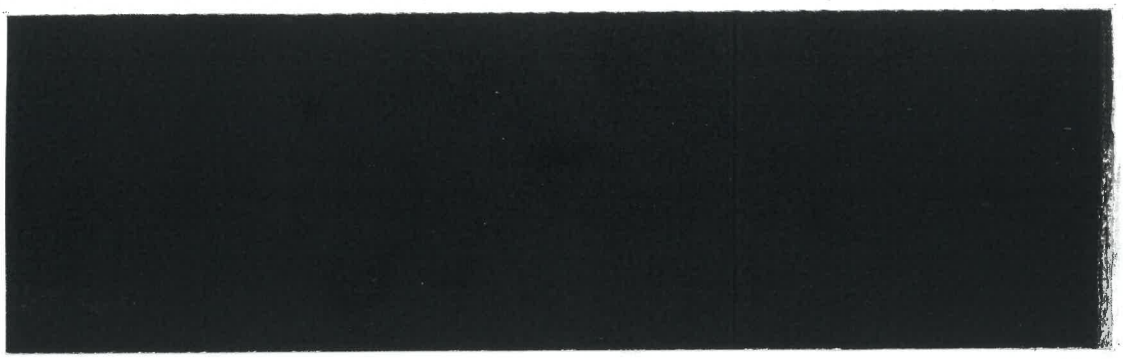
**Study Title: Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions.**

**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

On behalf of the Sponsor, I am aware of, and agree to comply with all procedures contained in this protocol according to Good Clinical Practice (GCP) (International Conference on Harmonisation (ICH) E6 (R2)) and the applicable regulatory requirements.

**Sponsor's representative:**



**By Erciyes University Hakan Cetinsaya GCP and Research Center (Clinical Unit)**

**Study Title: Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions.**

**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

**Investigator's statement:**

I have carefully read this protocol and I confirm it contains all necessary information required to conduct this study. I agree to conduct this clinical study as stated in the approved protocol according to Sponsor requirements, the European Directive 2001/20/EC, the European Regulation 536/2014, GCP requirements as contained in ICH guidelines E6 (R2), the ethical principles that have their origins in the Declaration of Helsinki and all amendments. I agree to allow the Sponsor (or delegates) and applicable Regulatory Authorities to inspect the study facilities and pertinent records at reasonable times and in a reasonable manner to ensure subject confidentiality.

**Principal Investigator:**

[redacted]

**Co-Investigators:**

[redacted]

**By Anapharm Europe, S.L.U. (Global CRO)**

**Study Title: Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions.**

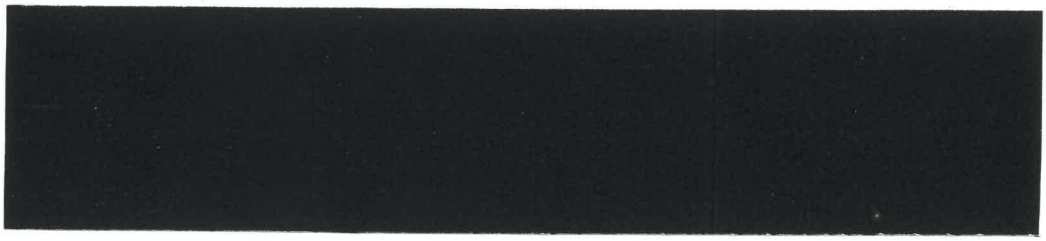
**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

I am aware of, and agree to comply with all study procedures contained in this protocol.

**Clinical Services – Clinical Services Director:**

**Quality Assurance Unit Director:**



**By Anapharm Europe, S.L.U. (Global CRO)**

Bioanalytical Laboratory:

**Study Title: Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions.**

**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

The bioanalytical laboratory agrees to conduct all study-related bioanalytical procedures as stated in the approved protocol according to the GLP-OECD Principles of Good Laboratory Practice (GLP) and applicable European Medicines Agency (EMA) guidelines and to allow the Sponsor (or delegates) and applicable Regulatory Authorities to inspect the study facilities and pertinent records at reasonable times and in a reasonable manner to ensure subject confidentiality.

**Small Molecule Operations Director:**

**By Medical Statistics Core Facility, IDIBAPS – Hospital Clinic Barcelona (Statistics Facility)**

**Study Title: Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions.**

**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

I am aware of, and agree to comply with all study procedures contained in this protocol.

**Project Statistician:**

[redacted]

## 4. STUDY ADMINISTRATIVE STRUCTURE

| | |
|---|---|
| **Sponsor:** | PrJSC "Pharmaceutical firm "Darnitsa"<br>02093, 13, Boryspilska str., Kyiv, Ukraine |
| Sponsor's Representative: | [redacted] |
| Qualified Person for Pharmacovigilance (QPPV) | [redacted] |
| **Clinical Unit:** | Erciyes University Hakan Cetinsaya GCP and Research Center |
| Principal Investigator: | [redacted] |
| Co-Investigators: | [redacted] |

| | |
|---|---|
| **Clinical Laboratory:** | [redacted]<br>Erciyes University Central Laboratory / Faculty of Medicine [redacted] |
| **COVID-19 Tests:**<br>(Coronavirus disease – 19) | [redacted]<br>Erciyes University, Department of medical microbiology / Faculty of Medicine<br>[redacted] |
| **Local CRO:** | [redacted]<br>IDEAL Biyolojik Ürünler ve İlaç Danışmanlık Eğitim Ltd. Şti./Pharma Consulting (IDEAL CRO)<br>[redacted] |
| **Global CRO: Clinical Services and Bioanalytical Laboratory** | Anapharm Europe, S.L.U.<br>[redacted] |
| Clinical Services – Clinical Services Director: | [redacted]<br>Anapharm Europe, S.L.U.<br>[redacted] |
| Clinical Services – Medical Writing and Data Management: | [redacted]<br>Anapharm Europe, S.L.U.<br>[redacted] |
| Authors of the Clinical Study Protocol (CSP): | [redacted]<br>Anapharm Europe, S.L.U. |
| Bioanalytical Laboratory – Small Molecule Operations Director: | [redacted]<br>Anapharm Europe, S.L.U.<br>[redacted] |

Quality Assurance Unit Director: [redacted]

Anapharm Europe, S.L.U.

[redacted]

**Project Statistician:** [redacted]

Medical Statistics Core Facility

IDIBAPS – Hospital Clinic Barcelona

[redacted]

**Clinical Study Monitor (CSM):** TBD

# 5. INTRODUCTION

## 5.1. Study Rationale

The present study is a comparative bioavailability study performed to assess BE between a Test medication (future generic product) and a Reference medication (marketed medicinal product) in healthy volunteers.

The evaluation of BE between Test medication and Reference medication will be based on the EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr** (1). Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their BAs (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable "in vivo" performance, i.e. similarity in terms of safety and efficacy.

The Reference medication already is an European Union (EU) marketed product available as Arcoxia® 120 mg film-coated tablets (FCT) [Marketing Authorisation Holder (MAH): UAB "Merck Sharp&Dohme", Lithuania]. For the purpose of registering this product, its efficacy and safety were proven in clinical trials. This product will therefore serve as a Reference and a basis for comparing the Test medication: Exib 120 mg FCT manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine).

## 5.2. Etoricoxib FCT Summary Information

The information provided below has been obtained from the Summary of Product Characteristics (SmPC) of the Reference study medication: Arcoxia® (2).

### 5.2.1. Therapeutic Indications

Arcoxia is indicated in adults and adolescents 16 years of age and older for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis.

Arcoxia is indicated in adults and adolescents 16 years of age and older for the short-term treatment of moderate pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

### 5.2.2. Posology and Method of Administration

*Posology*

As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Osteoarthritis

The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 60 mg once daily may increase efficacy. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Rheumatoid arthritis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Ankylosing spondylitis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Acute pain conditions

For acute pain conditions, etoricoxib should be used only for the acute symptomatic period.

Acute gouty arthritis

The recommended dose is 120 mg once daily. In clinical trials for acute gouty arthritis, etoricoxib was given for 8 days.

Postoperative dental surgery pain

The recommended dose is 90 mg once daily, limited to a maximum of 3 days. Some patients may require other postoperative analgesia in addition to Arcoxia during the three day treatment period.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

The dose for OA should not exceed 60 mg daily.

The dose for RA and ankylosing spondylitis should not exceed 90 mg daily.

The dose for acute gout should not exceed 120 mg daily, limited to a maximum of 8 days treatment.

The dose for postoperative acute dental surgery pain should not exceed 90 mg daily, limited to a maximum of 3 days.

Special populations

Elderly patients

No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.

Patients with hepatic impairment

Regardless of indication, in patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), regardless of indication, the dose of 30 mg once daily should not be exceeded.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contra-indicated in these patients.

Patients with renal impairment

No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min. The use of etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated.

Paediatric population

Etoricoxib is contra-indicated in children and adolescents under 16 years of age.

*Method of administration*

Arcoxia is administered orally and may be taken with or without food. The onset of the effect of the medicinal product may be faster when Arcoxia is administered without food. This should be considered when rapid symptomatic relief is needed.

### 5.2.3. Pharmacodynamic Properties

Its pharmacotherapeutic group is anti-inflammatory and antirheumatic products, non-steroids, coxibs.

*Mechanism of Action*

Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

Across clinical pharmacology studies, Arcoxia produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

*Clinical efficacy and safety*

*Efficacy*

In patients with osteoarthritis (OA), etoricoxib 60 mg once daily provided significant improvements in pain and patient assessments of disease status. These beneficial effects were observed as early as the second day of therapy and maintained for up to 52 weeks. Studies with etoricoxib 30 mg once daily demonstrated efficacy superior to placebo over a 12 week treatment period (using similar assessments as the above studies). In a dose ranging study, etoricoxib 60 mg demonstrated significantly greater improvement than 30 mg for all 3 primary endpoints over 6 weeks of treatment. The 30 mg dose has not been studied in osteoarthritis of hands.

In patients with rheumatoid arthritis (RA), etoricoxib 60 mg and 90 mg once daily both provided significant improvements in pain, inflammation, and mobility. In studies evaluating the 60 mg and 90 mg dose, these beneficial effects were maintained over the 12-week treatment periods. In a study evaluating the 60 mg dose compared to the 90 mg dose, etoricoxib 60 mg once daily and 90 mg once daily were both more effective than placebo. The 90 mg dose was superior to the 60 mg dose for Patient Global Assessment of Pain (0-100mm visual analogue scale), with an average improvement of -2.71 mm (95% CI: -4.98 mm, -0.45 mm).

In patients experiencing attacks of acute gouty arthritis, etoricoxib 120 mg once daily over an eight-day treatment period, relieved moderate to extreme joint pain and inflammation comparable to indomethacin 50 mg three times daily. Pain relief was observed as early as four hours after initiation of treatment.

In patients with ankylosing spondylitis, etoricoxib 90 mg once daily provided significant improvements in spine pain, inflammation, stiffness and function. The clinical benefit of etoricoxib was observed as early as the second day of therapy after initiation of treatment and was maintained throughout the 52-week treatment period. In a second study evaluating the 60 mg dose compared to the 90 mg dose, etoricoxib 60 mg daily and 90 mg daily demonstrated similar efficacy compared to naproxen 1,000 mg daily. Among inadequate responders to 60 mg daily for 6 weeks, dose escalation to 90 mg daily improved spinal pain intensity score (0-100 mm visual analogue scale) compared to continuing on 60 mg daily, with an average improvement of -2.70 mm (95% CI: -4.88 mm, -0.52 mm).

In a clinical study evaluating postoperative dental pain, etoricoxib 90 mg was administered once daily for up to three days. In the subgroup of patients with moderate pain at baseline, etoricoxib 90 mg demonstrated a similar analgesic effect to that of ibuprofen 600 mg (16.11 vs. 16.39; P=0.722), and greater than that of paracetamol/codeine 600 mg/60 mg (11.00; P<0.001) and placebo (6.84; P<0.001) as measured by total pain relief over the first 6 hours (TOPAR6). The proportion of patients reporting rescue medication usage within the first 24 hours of dosing was 40.8% for etoricoxib 90 mg, 25.5% for ibuprofen 600 mg Q6h, and 46.7% for paracetamol/codeine 600 mg/60 mg Q6h compared to 76.2% for placebo. In this study, the median onset of action (perceptible pain relief) of 90 mg etoricoxib was 28 minutes after dosing.

*Safety*

*Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Programme*

The MEDAL Programme was a prospectively designed Cardiovascular Safety Outcomes Programme of pooled data from three randomized, double-blind active comparator controlled trials, the MEDAL study, EDGE II and EDGE.

The MEDAL Study, was an endpoint driven Cardiovascular Outcomes study in 17,804 OA and 5,700 RA patients treated with etoricoxib 60 (OA) or 90 mg (OA and RA) or diclofenac 150 mg daily for a mean period of 20.3 months (maximum of 42.3 months, median 21.3 months). In this trial, only serious adverse events and discontinuations due to any adverse events were recorded.

The EDGE and EDGE II studies compared the gastrointestinal tolerability of etoricoxib versus diclofenac. The EDGE study included 7,111 OA patients treated with a dose of etoricoxib 90 mg daily (1.5 times the dose recommended for OA) or diclofenac 150 mg daily for a mean period of 9.1 months (maximum 16.6 months, median 11.4 months). The EDGE II study included 4,086 RA patients treated with etoricoxib 90 mg daily or diclofenac 150 mg daily for a mean period of 19.2 months (maximum 33.1 months, median 24 months).

In the pooled MEDAL Programme, 34,701 patients with OA or RA were treated for a mean duration of 17.9 months (maximum 42.3 months, median 16.3 months) with approximately 12,800 patients receiving treatment for more than 24 months. Patients enrolled in the Programme had a wide range of cardiovascular and gastrointestinal risk factors at baseline. Patients with a recent history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention within 6 months preceding enrolment were excluded. Use of gastroprotective agents and low dose aspirin were permitted in the studies.

Overall Safety:

There was no significant difference between etoricoxib and diclofenac in the rate of cardiovascular thrombotic events. Cardiorenal adverse events were observed more frequently with etoricoxib than with diclofenac, and this effect was dose-dependent (see specific results below). Gastrointestinal and hepatic adverse events were observed significantly more frequently with diclofenac than etoricoxib. The incidence of adverse experiences in EDGE and EDGE II and of adverse experiences considered serious or resulting in discontinuation in the MEDAL study was higher with etoricoxib than diclofenac.

Cardiovascular safety results:

The rate of confirmed thrombotic cardiovascular serious adverse events (consisting of cardiac, cerebrovascular, and peripheral vascular events) was comparable between etoricoxib and diclofenac, and data are summarized in the table below. There were no statistically significant differences in thrombotic event rates between etoricoxib and diclofenac across all subgroups analyzed including patient categories across a range of baseline cardiovascular risk. When

considered separately, the relative risks for confirmed thrombotic cardiovascular serious adverse events with etoricoxib 60 mg or 90 mg compared with diclofenac 150 mg were similar.

**Rates of Confirmed Thrombotic Cardiovascular Events (Pooled MEDAL Programme)**

| | Etoricoxib (N=16,819) 25,836 Patient-Years | Diclofenac (N=16,483) 24,766 Patient-Years | Between Treatment Comparison |
|---|---|---|---|
| | Rate† (95% CI) | Rate† (95% CI) | Relative Risk (95% CI) |
| **Confirmed Thrombotic Cardiovascular Serious Adverse Events** | | | |
| Per-protocol | 1.24 (1.11, 1.38) | 1.30 (1.17, 1.45) | 0.95 (0.81, 1.11) |
| Intent-to-treat | 1.25 (1.14, 1.36) | 1.19 (1.08, 1.30) | 1.05 (0.93, 1.19) |
| **Confirmed Cardiac Events** | | | |
| Per-protocol | 0.71 (0.61, 0.82) | 0.78 (0.68, 0.90) | 0.90 (0.74, 1.10) |
| Intent-to-treat | 0.69 (0.61, 0.78) | 0.70 (0.62, 0.79) | 0.99 (0.84, 1.17) |
| **Confirmed Cerebrovascular Events** | | | |
| Per-protocol | 0.34 (0.28, 0.42) | 0.32 (0.25, 0.40) | 1.08 (0.80, 1.46) |
| Intent-to-treat | 0.33 (0.28, 0.39) | 0.29 (0.24, 0.35) | 1.12 (0.87, 1.44) |
| **Confirmed Peripheral Vascular Events** | | | |
| Per-protocol | 0.20 (0.15, 0.27) | 0.22 (0.17, 0.29) | 0.92 (0.63, 1.35) |
| Intent-to-treat | 0.24 (0.20, 0.30) | 0.23 (0.18, 0.28) | 1.08 (0.81, 1.44) |

†Events per 100 Patient-Years; CI=confidence interval
N=total number of patients included in Per-protocol population
Per-protocol: all events on study therapy or within 14 days of discontinuation (excluded: patients who took < 75% of their study medication or took non-study NSAIDs >10% of the time).
Intent-to-treat: all confirmed events up to the end of the trial (included patients potentially exposed to non-study interventions following discontinuation of study medication). Total number of patients randomised, n= 17,412 on etoricoxib and 17,289 on diclofenac.

Cardiovascular mortality, as well as overall mortality, was similar between the etoricoxib and diclofenac treatment groups.

Cardiorenal Events:

Approximately 50% of patients enrolled in the MEDAL study had a history of hypertension at baseline. In the study, the incidence of discontinuations due to hypertension-related adverse events was statistically significantly higher for etoricoxib than for diclofenac. The incidence of congestive heart failure adverse events (discontinuations and serious events) occurred at similar rates on etoricoxib 60 mg compared to diclofenac 150 mg but was higher for etoricoxib 90 mg compared to diclofenac 150 mg (statistically significant for 90 mg etoricoxib vs. 150 mg diclofenac in MEDAL OA cohort). The incidence of confirmed congestive heart failure adverse events (events that were serious and resulted in hospitalisation or a visit to an emergency department) was non-significantly higher with etoricoxib than diclofenac 150 mg, and this effect was dose-dependent. The incidence of discontinuations due to oedema-related adverse events was higher for etoricoxib than diclofenac 150 mg, and this effect was dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg).

The cardiorenal results for EDGE and EDGE II were consistent with those described for the MEDAL Study.

In the individual MEDAL Programme studies, for etoricoxib (60 mg or 90 mg), the absolute incidence of discontinuation in any treatment group was up to 2.6% for hypertension, up to 1.9%

for oedema, and up to 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg.

MEDAL Programme Gastrointestinal Tolerability Results:

A significantly lower rate of discontinuations of treatment for any clinical (e.g., dyspepsia, abdominal pain, ulcer) GI adverse event was observed with etoricoxib compared with diclofenac within each of the three component studies of the MEDAL Programme. The rates of discontinuations due to adverse clinical GI events per hundred patient-years over the entire period of study were as follows: 3.23 for etoricoxib and 4.96 for diclofenac in the MEDAL Study; 9.12 with etoricoxib and 12.28 with diclofenac in the EDGE study; and 3.71 with etoricoxib and 4.81 with diclofenac in the EDGE II study.

MEDAL Programme Gastrointestinal Safety Results:

Overall upper GI events were defined as perforations, ulcers and bleeds. The subset of overall upper GI events considered complicated included perforations, obstructions, and complicated bleeding; the subset of upper GI events considered uncomplicated included uncomplicated bleeds and uncomplicated ulcers. A significantly lower rate of overall upper GI events was observed with etoricoxib compared to diclofenac. There was no significant difference between etoricoxib and diclofenac in the rate of complicated events. For the subset of upper GI haemorrhage events (complicated and uncomplicated combined), there was no significant difference between etoricoxib and diclofenac. The upper GI benefit for etoricoxib compared with diclofenac was not statistically significant in patients taking concomitant low-dose aspirin (approximately 33% of patients).

The rates per hundred patient-years of confirmed complicated and uncomplicated upper GI clinical events (perforations, ulcers and bleeds (PUBs)) were 0.67 (95% CI 0.57, 0.77) with etoricoxib and 0.97 (95% CI 0.85, 1.10) with diclofenac, yielding a relative risk of 0.69 (95% CI 0.57, 0.83).

The rate for confirmed upper GI events in elderly patients was evaluated and the largest reduction was observed in patients ≥ 75 years of age (1.35 [95% CI 0.94, 1.87] vs. 2.78 [95% CI 2.14, 3.56] events per hundred patient-years for etoricoxib and diclofenac, respectively.

The rates of confirmed lower GI clinical events (small or large bowel perforation, obstruction, or haemorrhage, (POBs)) were not significantly different between etoricoxib and diclofenac.

MEDAL Programme Hepatic Safety Results:

Etoricoxib was associated with a statistically significantly lower rate of discontinuations due to hepatic-related adverse experiences than diclofenac. In the pooled MEDAL Programme, 0.3% of patients on etoricoxib and 2.7% of patients on diclofenac discontinued due to hepatic-related adverse experiences. The rate per hundred patient-years was 0.22 on etoricoxib and 1.84 for diclofenac (p-value was <0.001 for etoricoxib vs. diclofenac). However, most hepatic adverse experiences in the MEDAL Programme were non-serious.

*Additional Thrombotic Cardiovascular Safety Data*

In clinical studies excluding the MEDAL Programme Studies, approximately 3,100 patients were treated with etoricoxib ≥60 mg daily for 12 weeks or longer. There was no discernible difference in the rate of confirmed serious thrombotic cardiovascular events between patients receiving etoricoxib ≥60 mg, placebo, or non-naproxen NSAIDs. However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and selective COX-2 inhibitors may be of clinical significance in patients at risk of thrombo-embolic events. Selective COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

*Additional Gastrointestinal Safety Data*

In two 12-week double-blind endoscopy studies, the cumulative incidence of gastroduodenal ulceration was significantly lower in patients treated with etoricoxib 120 mg once daily than in patients treated with either naproxen 500 mg twice daily or ibuprofen 800 mg three times daily. Etoricoxib had a higher incidence of ulceration as compared to placebo.

*Renal Function Study in the Elderly*

A randomized, double-blind, placebo-controlled, parallel-group study evaluated the effects of 15 days of treatment of etoricoxib (90 mg), celecoxib (200 mg bid), naproxen (500 mg bid) and placebo on urinary sodium excretion, blood pressure, and other renal function parameters in subjects 60 to 85 years of age on a 200-mEq/day sodium diet. Etoricoxib, celecoxib, and naproxen had similar effects on urinary sodium excretion over the 2 weeks of treatment. All active comparators showed an increase relative to placebo with respect to systolic blood pressures; however, etoricoxib was associated with a statistically significant increase at Day 14 when compared to celecoxib and naproxen (mean change from baseline for systolic blood pressure: etoricoxib 7.7 mmHg, celecoxib 2.4 mmHg, naproxen 3.6 mmHg).

### 5.2.4. Pharmacokinetic Properties

*Absorption*

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean $C_{max}$ = 3.6 µg/ml) was observed at approximately 1 hour ($T_{max}$) after administration to fasted adults. The geometric mean area under the curve ($AUC_{0-24hr}$) was 37.8 µg•hr/ml. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36% decrease in $C_{max}$ and an increase in $T_{max}$ by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

*Distribution*

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state ($V_{dss}$) was approximately 1,20l in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

*Biotransformation*

Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles in vivo have not been studied.

Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

*Elimination*

Following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min.

*Characteristics in patients*

Elderly patients: Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young.

Gender: The pharmacokinetics of etoricoxib are similar between men and women.

Hepatic impairment: Patients with mild hepatic dysfunction (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7-9) administered etoricoxib 60 mg every other day had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10).

Renal impairment: The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min).

Paediatric patients: The pharmacokinetics of etoricoxib in paediatric patients (<12 years old) have not been studied.

In a pharmacokinetic study (n=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established.

### 5.2.5. Contraindications, Interactions, Overdose and Special Warnings for Use

*Contraindications*

- Hypersensitivity to the active substance or to any of the excipients in the Arcoxia formulation.
- Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions.
- Pregnancy and lactation.
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).
- Estimated renal creatinine clearance <30 ml/min.
- Children and adolescents under 16 years of age.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

*Interactions*

Pharmacodynamic interactions

Oral anticoagulants: In subjects stabilised on chronic warfarin therapy, the administration of etoricoxib 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalised Ratio (INR). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Acetylsalicylic Acid: In a study in healthy subjects, at steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

Cyclosporin and tacrolimus: Although this interaction has not been studied with etoricoxib, coadministration of cyclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when etoricoxib and either of these drugs is used in combination.

Pharmacokinetic interactions

The effect of etoricoxib on the pharmacokinetics of other drugs:

Lithium: NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Methotrexate: Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. In one study, etoricoxib 120 mg had no effect, but in the other study, etoricoxib 120 mg increased methotrexate plasma concentrations by 28% and reduced renal clearance of methotrexate by 13%. Adequate monitoring for methotrexate-related toxicity is recommended when etoricoxib and methotrexate are administered concomitantly.

Oral contraceptives: Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for

use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

Hormone Replacement Therapy (HRT): Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN™) for 28 days, increased the mean steady state $AUC_{0-24hr}$ of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). The effect of the recommended chronic doses of etoricoxib (30, 60, and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure ($AUC_{0-24hr}$) to these estrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib because the increase in oestrogen exposure might increase the risk of adverse events associated with HRT.

Prednisone/prednisolone: In drug-interaction studies, etoricoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone.

Digoxin: Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady-state plasma $AUC_{0-24hr}$ or renal elimination of digoxin. There was an increase in digoxin $C_{max}$ (approximately 33%). This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Effect of etoricoxib on drugs metabolised by sulfotransferases

Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g., oral salbutamol and minoxidil).

Effect of etoricoxib on drugs metabolised by CYP isoenzymes

Based on in vitro studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

Effects of other drugs on the pharmacokinetics of etoricoxib

The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles have not been studied in vivo.

Ketoconazole: Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers, did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC).

Voriconazole and Miconazole: Co-administration of either oral voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with etoricoxib caused a slight increase in exposure to etoricoxib, but is not considered to be clinically meaningful based on published data.

Rifampicin: Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations. This interaction may result in recurrence of symptoms when etoricoxib is co-administered with rifampicin. While this information may suggest an increase in dose, doses of etoricoxib greater than those listed for each indication have not been studied in combination with rifampicin and are therefore not recommended.

Antacids: Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent.

*Overdose*

In clinical studies, administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.

Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

*Special Warnings for Use*

Gastrointestinal effects

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with etoricoxib.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials.

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration.

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued.

Renal effects

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Fluid retention, oedema and hypertension

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic effects

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with etoricoxib 30, 60 and 90 mg daily.

Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

General

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered. Medically appropriate supervision should be maintained when using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

Caution should be used when initiating treatment with etoricoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance. Patients appear to be at highest risk for these reactions early in the course of therapy with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Etoricoxib may mask fever and other signs of inflammation.

Caution should be exercised when co-administering etoricoxib with warfarin or other oral anticoagulants.

The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive.

Arcoxia tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 5.2.6. Undesirable Effects

*Summary of the safety profile*

In clinical trials, etoricoxib was evaluated for safety in 9,295 individuals, including 6,757 patients with OA, RA, chronic low back pain or ankylosing spondylitis (approximately 600 patients with OA or RA were treated for one year or longer).

In clinical studies, the undesirable effects profile was similar in patients with OA or RA treated with etoricoxib for one year or longer.

In a clinical study for acute gouty arthritis, patients were treated with etoricoxib 120 mg once daily for eight days. The adverse experience profile in this study was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In a cardiovascular safety outcomes programme of pooled data from three active comparator controlled trials, 17, 412 patients with OA or RA were treated with etoricoxib (60 mg or 90 mg) for a mean duration of approximately 18 months.

In clinical studies for acute postoperative dental pain following surgery including 614 patients treated with etoricoxib (90 mg or 120 mg), the adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

*Tabulated list of adverse reactions*

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with etoricoxib 30 mg, 60 mg or 90 mg up to the recommended dose for up to 12 weeks; in the MEDAL Programme studies for up to 3½ years; in short term acute pain studies for up to 7 days; or in post-marketing experience:

| System Organ Class | Adverse Reactions | Frequency Category* |
|---|---|---|
| Infections and infestations | alveolar osteitis | Common |
| | gastroenteritis, upper respiratory infection, urinary tract infection | Uncommon |
| Blood and lymphatic system disorders | anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia | Uncommon |
| Immune system disorders | hypersensitivity‡ ß | Uncommon |
| | angioedema/anaphylactic /anaphylactoid reactions including shock‡ | Rare |
| Metabolism and nutrition disorders | oedema/fluid retention | Common |
| | appetite increase or decrease, weight gain | Uncommon |
| Psychiatric disorders | anxiety, depression, mental acuity decreased, hallucinations‡ | Uncommon |
| | confusion‡, restlessness‡ | Rare |
| Nervous system disorders | dizziness, headache | Common |
| | dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence | Uncommon |
| Eye disorders | blurred vision, conjunctivitis | Uncommon |
| Ear and labyrinth disorders | tinnitus, vertigo | Uncommon |
| Cardiac disorders | palpitations, arrhythmia‡ | Common |
| | atrial fibrillation, tachycardia‡, congestive heart failure, non-specific ECG changes, angina pectoris‡, myocardial infarction§ | Uncommon |
| Vascular disorders | hypertension | Common |
| | flushing, cerebrovascular accident§, transient ischaemic attack, hypertensive crisis‡, vasculitis‡ | Uncommon |
| Respiratory, thoracic and mediastinal disorders | bronchospasm‡ | Common |
| | cough, dyspnoea, epistaxis | Uncommon |

| | | |
|---|---|---|
| Gastrointestinal disorders | abdominal pain | Very common |
| | Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer | Common |
| | abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis‡ | Uncommon |
| Hepatobiliary disorders | ALT increased, AST increased | Common |
| | hepatitis‡ | Rare |
| | hepatic failure‡, jaundice‡ | Rare† |
| Skin and subcutaneous tissue disorders | ecchymosis | Common |
| | facial oedema, pruritus, rash, erythema‡, urticaria‡ | Uncommon |
| | Stevens-Johnson syndrome‡, toxic epidermal necrolysis‡, fixed drug eruption‡ | Rare† |
| Musculoskeletal and connective tissue disorders | muscular cramp/spasm, musculoskeletal pain/stiffness | Uncommon |
| Renal and urinary disorders | proteinuria, serum creatinine increased, renal failure/renal insufficiency‡ | Uncommon |
| General disorders and administration site conditions | asthenia/fatigue, flu-like disease | Common |
| | chest pain | Uncommon |
| Investigations | blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased | Uncommon |
| | blood sodium decreased | Rare |

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).
‡ This adverse reaction was identified through post-marketing surveillance. Its reported frequency has been estimated based upon the highest frequency observed across clinical trial data pooled by indication and approved dose.
†The frequency category of "Rare" was defined per the Summary of Product Characteristics (SmPC) guidance (rev. 2, Sept 2009) on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of subjects treated with Arcoxia in the analysis of the Phase III data pooled by dose and indication (n=15,470).
ß Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and "nonspecific allergy".
§Based on analyses of long-term placebo and active controlled clinical trials, selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke. The absolute risk increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome.

# 6. STUDY OBJECTIVES

## 6.1. Primary Objective

To evaluate and compare the BA and therefore to assess the BE between a Test formulation of Exib 120 mg FCT manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine) and a Reference formulation of Arcoxia® 120 mg FCT manufactured by Merck Sharp&Dohme B.V. (The Netherlands) when administered orally at the same dose level to 28 healthy volunteers under fasting conditions, in a 2-way crossover design.

## 6.2. Secondary Objective

To assess the safety and tolerability of both Test and Reference formulations.

# 7. STUDY DESIGN

This is an open-label, two-period, two-sequence, two-way crossover, randomised, single dose bioequivalence study in healthy male volunteers under fasting conditions. Treatment periods will be separated with a washout period of at least 14 days.

Each subject will be randomly assigned to receive one FCT of either Test or Reference medication on Day 1 of each study period. Randomisation will be performed in accordance with the study randomisation list.

The estimated duration of the clinical phase of the study is expected not to exceed 23 days, comprising 5 days of screening period and at least 14 days of washout period. The follow up (FU) visit will be performed before the subject leaves the Clinical Unit (CU) after the last PK blood sample in Period 2 has been collected.

Subjects will remain in confinement from Day -5 of Screening until the FU visit (5 days prior to the first study administration until 3 days post last dose in Period 2). Therefore, the maximum planned duration of confinement in this study is 23 days and 22 nights.

Clinical procedures to be carried out over the course of the study are presented in Section 11.

The end of the clinical phase is defined as the last subject last visit (LSLV).

## 7.1. Discussion of Study Design and Choice of Volunteers

### 7.1.1. Study Design

To determine the most appropriate study design for the Investigational Medicinal Product (IMP) being tested, data on the elimination half-life and intra-subject variability of the primary pk parameters of etoricoxib were reviewed (2).

Since etoricoxib is not a long half-life drug and it does not exhibit highly variable pharmacokinetics, the recommended design for comparing the study formulations by the Guideline on the Investigation of Bioequivalence is the standard: Randomised, two-period, two-sequence single dose crossover study (1).

### 7.1.2. Study Dose

In accordance with the Guideline on the Investigation of Bioequivalence (1), a dose of 120 mg has been selected for the study as the IMP shows linear pharmacokinetics with no safety/tolerability concerns at this dose level (2).

### 7.1.3. Fasting/Fed Conditions

Study drug administration will be performed under fasting conditions as per Guideline on the Investigation of Bioequivalence (1), which states that products for which the SmPC recommends the intake of the Reference medication irrespective of food, bioequivalence studies should be carried out in the fasted state as it is considered the most sensitive condition to detect a potential difference between formulations.

### 7.1.4. Choice of Volunteers

Only healthy volunteers will be enrolled in this study in accordance with the Guideline on the Investigation of Bioequivalence (1), which states that healthy subjects are regarded as an adequate population to reduce variability not related to differences between products and also allow extrapolation of the results to populations for which the reference medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.).

The study eligibility criteria have been chosen to only allow participation of males.

As the present study is intended for European registration, where the representative race of the general adult population is Caucasian, only Caucasian subjects will be enrolled in this study.

According to the EMA Guideline (1), subjects should be at least 18 years old to participate in the study. Elderly subjects (i.e. over 55 years of age) will not be eligible for this study as they are likely to have a high incidence of AEs due to higher plasma levels of etoricoxib when compared to adults (2).

In accordance with the EMA Guideline (1), subjects should preferably have a BMI between 18.5 and 30 kg/m$^2$ to participate in the study. These BMI limits are commonly used as an enrolment criteria for studies in healthy volunteers and are therefore considered adequate for this study.

### 7.1.5. Choice of Analyte

The assessment of BE will be based on the plasma drug levels of etoricoxib parent drug in this study. This approach is in line with the EMA Guideline on Bioequivalence studies and it is based on the rationale that the parent drug is the most sensitive analyte to detect differences in the concentration-time profile between the study formulations (1).

### 7.1.6. Pk Sampling Schedule

The study pk sampling schedule has been planned to ensure frequent sampling around predicted $t_{max}$ of etoricoxib following a single oral administration. Samples will be collected up to 72 hours post-dose to provide a reliable estimate of the extent of exposure to etoricoxib (2). Further details on pk sampling schedule are provided in Section 14.1.

### 7.1.7. Washout Period

Based on the $t_{1/2}$ of etoricoxib (22 hours) (2), a washout period of at least 14 days has been selected to ensure the IMP is completely eliminated from the body between study periods.

Washout period will occur between Day 1 Period 1 and Day 1 Period 2. Subjects will remain in confinement at the CU during the washout period and repeated forehead body temperature measurements will be taken.

### 7.1.8. COVID-19 RT-PCR Tests

Due to COVID-19's (Coronavirus disease – 19) pandemic safety measures, subjects will be confined during four nights in a hotel near the CU ([redacted] before Day -1 in Period 1. A total of three COVID-19 RT-PCR Tests will be performed on Day -5, Day -2 of screening and the day before subject's discharge from the CU as part of the FU visit. Repeated forehead body temperature measurements will be taken throughout the confinement.

In case of positive result for any COVID-19 RT-PCR test, it will be notified to Turkish Ministry of Health for further safety actions out of the study's scope.

## 7.2. Measures to Minimise Bias

The following measures to reduce bias will be implemented:

- Subjects will be sequentially assigned to receive either Test or Reference product in a random fashion.
- Eligibility of subjects will be based on the fulfilment of all study inclusion and exclusion criteria.
- The CU staff will monitor and record subject's compliance and any non-compliance with the protocol requirements.

The Bioanalytical Laboratory staff will not have access to the study randomisation list.

# *8. ELIGIBILITY OF SUBJECTS*

The below eligibility criteria have been set for the study:

## 8.1. Inclusion Criteria

Volunteers must meet all of the following criteria to be eligible for enrolment in the study:

1. Caucasian males.
2. Subjects aged between 18 and 55 years (inclusively) at the date of signing Informed Consent Form (ICF) which is defined as the beginning of the screening period.
3. Subjects must have a BMI at screening within 18.5 to 30.0 kg/m$^2$, inclusively.
4. Willingness to adhere to the protocol requirements and to provide written, personally signed, and dated ICF to participate in the study before the start of any study-related procedures.
5. Availability for the entire duration of the study.

6. Motivated subjects with absence of intellectual problems likely to limit the validity of consent to participate in the study or the compliance with protocol requirements; ability to cooperate adequately; ability to understand and observe the instructions of the physician or designee.
7. Satisfactory medical assessment at screening with no clinically relevant abnormalities as determined by medical history, physical examination, ECG, and clinical laboratory evaluation (haematology, biochemistry and urinalysis) that are reasonably likely to interfere with the subject's participation in or ability to complete the study as assessed by the Investigator.
8. Subjects must agree to abstain from xanthine-containing products (i.e. coffee, tea, cola, energy drinks, chocolate, etc.) from 48 hours prior to the first study drug administration until the end of confinement.
9. Subjects must agree to abstain from poppy seed-containing products from 48 hours prior to the first study drug administration until the end of confinement.
10. Subjects must agree to abstain from alcohol from 48 hours prior to the first study drug administration until the end of study.
11. Subjects must not consume and agree to continue to abstain from St John's Wort, vitamins and herbal remedies from 2 weeks prior to the first study drug administration until the end of confinement.
12. Subjects must not consume and agree to continue to abstain from beverages or food containing orange, grapefruit or pomelo from 2 weeks prior to the first study drug administration until the end of confinement.
13. Subjects must agree to use medically acceptable methods of contraception during the study and for 30 days after the end of the study. Medically acceptable methods of contraception include using a condom with a female partner of childbearing potential who is using oral contraceptives, hormonal patch, implant or injection, intrauterine device, or diaphragm with spermicide. Complete abstinence alone can be used as a method of contraception.

## 8.2. Exclusion Criteria

Subjects will be excluded from enrolment in the study if they meet any of the following criteria:

1. History of significant hypersensitivity to etoricoxib or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (such as angioedema) to any drug.
2. Presence of significant gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects.
3. History of major surgery of the gastrointestinal tract except for appendectomy.
4. History of significant gastrointestinal, liver or kidney disease that may affect the drug BA.
5. Presence of significant cardiovascular, respiratory, genitourinary, musculoskeletal, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease.
6. Presence of respiratory infection symptoms (COVID-19 infection symptoms) like fever, dry cough, nasal congestion or sore throat.

7. Having COVID-19 infection or having been in contact to people with known COVID-19 infection in the last 14 days.
8. Use of tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes) within 6 months prior to Day 1 Period 1.
9. History of controlled or uncontrolled hypertension or clinically relevant systolic blood pressure (SBP), diastolic blood pressure (DBP) and/or heart rate (HR) readings outside the normal ranges at screening (Day -3) or prior to drug administration on Day 1 Period 1. Normal ranges are the following:
    - SBP: 90 to 140 mmHg
    - DBP: 60 to 90 mmHg
    - HR: 50 to 100 beats/min
10. Forehead body temperature readings outside the range of 35.5 to 37.4ºC at screening (Day -5, -4, -3, -2, -1) or prior to the first drug administration.
11. Any planned surgery involving general, spinal or epidural anaesthesia from 3 months prior to Day 1 Period 1 to 7 days after last dosing.
12. Known presence of rare hereditary problems of galactose and/or lactose intolerance, lactase deficiency or glucose-galactose malabsorption.
13. Any clinically significant illness within 30 days prior to Day 1 Period 1.
14. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and Human Immunodeficiency Virus (HIV) antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampicin) within 30 days prior to Day 1 Period 1.
15. Use of Over the Counter (OTC) medications within 7 days prior to Day 1 Period 1. It will be specifically reminded that this includes cold preparations, acetylsalicylic acid (ASA), natural products used for therapeutic benefits and antacid preparations.
16. Intake of any prescription medication within 30 days prior to Day 1 Period 1.
17. Maintenance therapy with any drug or significant history of drug dependency.
18. Alcohol abuse, i.e. regular use of more than 10 units per week (one unit of alcohol equals 250 mL of beer, 125 mL of wine or 25 mL of spirits), a history of alcoholism or recovered alcoholics.
19. Positive alcohol, drugs of abuse or cotinine results at screening (Day -1).
20. Positive result on Day -5 and/or Day -2 of screening on COVID-19 RT-PCR test.
21. History of drug abuse or use of illegal drugs: use of soft drugs (e.g. marihuana) within 6 months of screening or hard drugs (e.g. amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opioids) within 1 year of screening.
22. A positive Human Immunodeficiency Virus antibody (HIV-Ab) screen, Hepatitis B surface antigen (HBsAg) or Hepatitis C Virus (HCV) tests.
23. Use of an investigational product within 60 days prior to Day 1 Period 1 or active enrolment in another drug or vaccine clinical study.

24. Use of depot injectable solutions with a half-life of >1 week within 6 months prior to Day 1 Period 1.
25. Subjects previously randomised in this study.
26. An inability to follow a standardised diet and meal schedule or inability to fast, as required during the study.
27. Donation of blood (at least 100 mL) or plasma by plasmapheresis within 30 days prior to Day 1 Period 1.
28. Volunteers who report difficulty swallowing tablets as a whole.

### 8.3. Discontinuation Criteria

Subjects will be allowed to discontinue their participation from the study at any time for any reason. A subject may also be discontinued to protect their health or the integrity of the study if necessary. The reason, date and time of withdrawal or termination will be documented in the subject's Case Report Form (CRF) and in the Clinical Study Report (CSR).

Subjects will be withdrawn from the study for any of the reasons below:

- A positive result to alcohol test performed at screening on Day -1.
- A positive result to drugs of abuse tests performed at screening on Day -1.
- A positive result to cotinine test performed at screening on Day -1.
- A positive result to COVID-19 RT-PCR test on Day -5 and/or Day -2 of screening.
- Clinically relevant SBP, DBP or HR readings outside the normal ranges on Day -3 or prior to study drug administration on Day 1 Period 1, as deemed by the Investigator. SBP, DBP and HR normal ranges are 90 to 140 mmHg, 60 to 90 mmHg and 50 to 100 beats/min, respectively.
- Forehead body temperature readings outside the range of 35.5 to 37.4 °C on Day -1 or prior to study drug administration on Day 1 Period 1.
- A subject who experiences emesis and/or severe diarrhoea within 2 hours (2 times expected median $t_{max}$) after study drug administration.
- Subject leaves the CU during confinement.

Subjects may also be withdrawn by the Principal Investigator (PI) or Co-Investigator for any of the following reasons:

- Significant AEs that could interfere with subject's safety.
- Significant protocol violations.
- Difficulties with blood collection.
- Subject is uncooperative during the study.
- Use of concomitant medications which at the Investigator's discretion, are reasonably likely to interfere with the study medication and may put the subject at risk.
- Intercurrent illness that can affect the BA of the study drug or may put the subject at risk.
- If the PI judges it is in the subject's best interest.

Subjects discontinuing the study after first dosing will not be replaced.

## 8.4. Restrictions

Prior to each drug administration, volunteers will be reminded of the study restrictions outlined in this section to ensure compliance. Subject's compliance will also be monitored throughout the study. If a subject is found to be non-compliant to any of these restrictions, it will be at the Investigator's (or delegate) discretion to decide whether the subject should remain in the study. Non-compliance with the below restrictions must be recorded.

### 8.4.1. Concomitant Medication

Subjects must not take any medication (including OTC) until the end of confinement. Should a subject take any concomitant medication after first drug administration, it will be at the Investigator's (or delegate) discretion to decide whether the volunteer should remain in the study, depending on the drug used, the time of drug intake, etc. The drug name, time of drug intake and dose administered must be recorded.

### 8.4.2. Alcohol

Subjects will be required to abstain from alcohol from 48 hours prior to the first study drug administration until the end of the study.

### 8.4.3. Nicotine Use

Subjects should be non-smokers or ex-smokers and should not smoke or use tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products until the end of confinement.

### 8.4.4. Xanthine and Poppy Seed-containing Products

Subjects will be required to avoid food or beverages containing xanthine (i.e. coffee, tea, cola, energy drinks, chocolate, etc.) and poppy seeds from 48 hours prior to the first study drug administration until the end of confinement.

### 8.4.5. Fluids

Fluid intake will be controlled for all subjects. Still water will be provided *ad libitum* until 1 hour pre-dose and from 4 hours post-dose. At 2 hours post-dose, 200 mL of still water will be provided.

During fluid restriction period (from 1 hour pre-dose to 4 hours post-dose), only 240 mL of still water given for dosing and 200 mL provided at 2 hours post-dose will be consumed.

### 8.4.6. Food

Food intake will be monitored and standardised throughout each confinement period for all subjects.

A standardised light dinner will be served on admission day (Day -1).

Subjects will be required to fast for at least 10 hours before each dosing and for 4 hours post-dose. Lunch and dinner will be served at 4 and 10 hours post-dose respectively. The same meals will be served on Day 1 of each study period.

#### 8.4.7. St John's Wort, Vitamins, Herbal Remedies, Orange, Grapefruit and/or Pomelo-containing Beverages and Food

Subjects will be required to avoid St John's Wort, vitamins, herbal remedies, food or beverages containing orange, grapefruit and/or pomelo from 2 weeks prior to the first study drug administration until the end of confinement.

#### 8.4.8. Posture and Physical Activity

Clinical procedures will be carried out in the sitting position except for drug administration, which will be performed while standing. However, should any AE occur, subjects may be placed in a different position. Subjects will remain under supervision and will not undertake any strenuous activity at any time throughout confinement period.

#### 8.4.9. Washroom Use

Washrooms will be locked for at least 4 hours after study drug administration. The use of the washroom facilities may be permitted only when it is completely necessary as long as subjects are accompanied by a member of clinical staff.

#### 8.4.10. Contraception

Subjects will be required to use medically acceptable methods of contraception during the study and for 30 days after the end of the study. Medically acceptable methods of contraception include using a condom with a female partner of childbearing potential who is using oral contraceptives, hormonal patch, implant or injection, intrauterine device, or diaphragm with spermicide. Complete abstinence alone can be used as a method of contraception.

## *9. RISK/BENEFIT EVALUATION*

Both Test and Reference products will be given to healthy subjects purely for research purposes and those subjects receiving the IMP will experience no medical benefit except for a general health examination performed during the trial.

Due to the nature of this study (i.e. assessment of bioequivalence between Test [Exib 120 mg FCT] and Reference medication [Arcoxia® 120 mg FCT], the risk of occurrence of Serious Adverse Events (SAEs) is reasonably low.

In order to prevent as much as possible the occurrence of any AE during the study, the following measures will be taken:

- Subjects with hypersensitivity reaction to etoricoxib or any related products (including excipients of the formulations) will not be eligible for enrolment in the study.
- The study inclusion/exclusion criteria have been carefully defined to ensure that only healthy adult male subjects are enrolled in the study.
- Subjects will remain under medical supervision in the CU throughout the study.
- The Investigator or delegate will check the safety and wellbeing of all study participants prior to discharge from the CU. Should a subject present any medical condition that requires

monitoring prior to discharge, volunteer's confinement period may be extended until the event is either resolved, a satisfactory explanation is found, or until the Investigator considers it is medically justifiable to terminate subject's confinement.

Due to COVID-19's pandemic, exceptional safety measures will be taken in order to prevent infections. Subjects will be isolated in a hotel [redacted] during four nights, they attend the CU to perform all screening procedures maintaining safety distance between them. As a standard safety procedure, on each admittance to the Clinical Unit, the body temperature will be measured. CU staff will use safety equipment (e.g. masks, gloves, glasses), volunteers could be split into groups, if necessary, in order to maintain safety distance between subjects and repeated forehead body temperature measurements will be performed during confinement.

## *10. STUDY TREATMENTS*

### 10.1. Test Medication (T)

| | |
|---|---|
| Name of the product: | Exib |
| Pharmaceutical form: | Film-coated tablets |
| Strength: | 120 mg |
| Content: | Active ingredient: etoricoxib<br>Excipients: core - calcium hydrogen phosphate, microcrystalline cellulose (type 112), croscarmellose sodium, crosspovidone (XL-10), sodium stearyl fumarate, talc; tablet coating - opadray II 85F green 85F210083 |
| Mode of administration: | Oral use |
| Manufacturer (country): | PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine) |

The batch number and retest date of the Test product will be included in the CSR.

### 10.2. Reference Medication (R)

| | |
|---|---|
| Name of the product: | Arcoxia |
| Pharmaceutical form: | Film-coated tablets |
| Strength: | 120 mg |
| Content: | Active ingredient: etoricoxib<br>Excipients: core - calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose; tablet coating - carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin, indigo carmine lake (E132), yellow ferric oxide (E172). |
| Mode of administration: | Oral use |
| Manufacturer (country): | Merck Sharp&Dohme B.V. (The Netherlands) |

| | |
|---|---|
| Country of purchase: | Lithuania |
| MAH: | UAB "Merck Sharp&Dohme", Lithuania |

The batch number and expiry date of the Reference product will be included in the CSR.

### 10.3. Study Randomisation List

The study randomisation list will be generated by the Project Statistician using the validated software proc Plan of SAS® System (release 9.4 or an upgraded version) (3) and will be based on the design, number of subjects and sequence of treatments to be administered in the study. The allocation of each treatment sequence to each subject will be done in such a way that the study is balanced. The Randomisation List will be signed and dated by the Project Statistician prior to implementation.

The randomisation list will not be made available to the Bioanalytical Laboratory staff during the study.

### 10.4. Packaging, Labelling and Storage of IMPs

The Sponsor is responsible for ensuring that T medication is manufactured in compliance with Good Manufacturing Practice (GMP) and that an adequate amount of both T and R medication is provided for the needs of the whole trial. The Sponsor is also responsible for keeping an appropriate amount of each study medication to allow for repeated pharmaceutical analysis if required.

PrJSC "Pharmaceutical firm "Darnitsa" will send the study medication along with certificates of analysis of both T and R products to the CU. The IMP will be released by the Sponsor's Qualified Person before shipment. Study medication must be transported and stored in the original primary package at a temperature not exceeding 25 °C for Test product in a secure, restricted access and temperature/humidity-controlled space in the CU. Temperature of transport and storage of IMPs will be continuously monitored using a data logger.

Packaging used for the transport of study medication to the CU is presented below:

**Labels of the Primary IMP Package (blister)**:

TEST:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*
Clinical Study Code: ETR01-E / 20ANE-3489C
Exib 120 mg film-coated tablets (T)
Quantity: 10 tablets in blister pack
Batch no. and expiry date are embossed on the blister
Storage conditions: in the original primary package at the temperature not exceeding 25° C.
Clinical Unit: Erciyes University Hakan Cetinsaya GCP and Research Center, Kayseri, Turkey
Manufacturer: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Global CRO: ANAPHARM EUROPE, S.L.U, Barcelona, Spain

REFERENCE:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*
Clinical Study Code: ETR01-E / 20ANE-3489C
ARCOXIA® 120 mg film-coated tablets (R)
Quantity: 7 tablets in blister pack
Batch no.: S033821
Expiry date: 05.2022
Storage conditions: store in the original package in order to protect from moisture
Clinical Unit: Erciyes University Hakan Cetinsaya GCP and Research Center, Kayseri, Turkey
Manufacturer: Merck Sharp & Dohme B.V., the Netherlands
Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Global CRO: ANAPHARM EUROPE, S.L.U, Barcelona, Spain

**Labels of the Secondary IMP Package (carton pack):**

a) T and R medications:

TEST:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*
Clinical Study Code: ETR01-E / 20ANE-3489C
Exib 120 mg film-coated tablets (T)
Quantity: 10 tablets in blister pack, 2 blisters in a carton pack. Total: 20 tablets
Batch no.: 010720
Expiry date: 07.2022
Storage conditions: in the original primary package at the temperature not exceeding 25° C.
Principal Investigator: [redacted]
Clinical Unit: Erciyes University Hakan Cetinsaya GCP and Research Center, Kayseri, Turkey
Manufacturer: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Global CRO: ANAPHARM EUROPE, S.L.U, Barcelona, Spain

REFERENCE:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*
Clinical Study Code: ETR01-E / 20ANE-3489C
ARCOXIA® 120 mg film-coated tablets (R)
Quantity: 7 tablets in blister pack, 2 blisters in a carton pack. Total: 14 tablets
Batch no.: S033821
Expiry date: 05.2022
Storage conditions: store in the original package in order to protect from moisture
Principal Investigator: [redacted]
Clinical Unit: Erciyes University Hakan Cetinsaya GCP and Research Center, Kayseri, Turkey
Manufacturer: Merck Sharp & Dohme B.V., the Netherlands
Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Global CRO: ANAPHARM EUROPE, S.L.U, Barcelona, Spain

No less than 72 study medication units (at least 36 Test and 36 Reference) will be provided in blisters (primary package) to account for:

- 28 units of Test and Reference product for the needs of the whole trial.
- 7 units of Test and Reference product as spare medication.
- 1 unit of Test and Reference product as sample medication.

Study medication will be individually packaged in the CU into labelled unit dose plastic bags (secondary packages) according to the randomisation scheme prior to each study period.

Study medication will be dispensed according to the CU Standard Operating Procedure [redacted] Blisters will be kept sealed until administration.

As per local regulation, the tear-off label to be used for the secondary package will have the detachable segment (which will be placed on the Case Report Form (CRF)) in English and the non-detachable part (which will remain on the package) in Turkish. Both segments of the label will contain the same details.

Templates of the IMP labels to be used for this study are presented below:

**Tear-off Labels of the Secondary IMP Package (individual plastic bag)**:

a) T and R medications:

TEST:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*
Global CRO: Anapharm Europe, S.L.U., [redacted]
Exib 120 mg film-coated tablets (T)
Dosage: 1 film-coated tablet
Clinical Study Code: 20ANE-3489C
Phase: Phase I (Bioequivalence)
Principal Investigator and Clinical Unit: [redacted]
Subject study number: Study period:
Treatment: T Batch no.:
Retest date:
Route of administration: Oral (with 240 mL of still water)
Manufacturer: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine
Storage conditions: In the original primary package not exceeding 25° C
Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

REFERENCE:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*

Global CRO: Anapharm Europe, S.L.U., [redacted]

ARCOXIA® 120 mg film-coated tablets (R)

Dosage: 1 film-coated tablet

Clinical Study Code: 20ANE-3489C

Phase: Phase I (Bioequivalence)

Principal Investigator and Clinical Uni[redacted])

Subject study number: Study period:

Treatment: R Batch no.:

Expiry date:

Route of administration: Oral (with 240 mL of still water)

Manufacturer: Merck Sharp & Dohme B.V., the Netherlands

Storage conditions: In the original package in order to protect from moisture

Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

b) T and R SPARE medications:

Spare TEST:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*

Global CRO: Anapharm Europe, S.L.U., [redacted]

Exib 120 mg film-coated tablets (T)

Dosage: 1 film-coated tablet

Clinical Study Code: 20ANE-3489C

Phase: Phase I (Bioequivalence)

Principal Investigator and Clinical Unit[redacted]

SPARE MEDICATION

Treatment: T Subject study number: Study period:

Retest date: Batch no.:

Route of administration: Oral (with 240 mL of still water)

Manufacturer: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

Storage conditions: In the original primary package not exceeding 25° C

Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

Spare REFERENCE:

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*

Global CRO: Anapharm Europe, [redacted]

ARCOXIA® 120 mg film-coated tablets (R)

Dosage: 1 film-coated tablet

Clinical Study Code: 20ANE-3489C

Phase: Phase I (Bioequivalence)

Principal Investigator and Clinical Unit: [redacted]

SPARE MEDICATION

Treatment: R | Subject study number: | Study period:

Expiry date: | Batch no.:

Route of administration: Oral (with 240 mL of still water)

Manufacturer: Merck Sharp & Dohme B.V., the Netherlands

Storage conditions: In the original package in order to protect from moisture

Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

c) T and R SAMPLE medications:

Sample TEST:

Sample medication details to be checked

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*

Global CRO: Anapharm Europe, [redacted]

Spain, +34 93 223 8636

Exib 120 mg film-coated tablets (T)

Dosage: 1 film-coated tablet

Clinical Study Code: 20ANE-3489C

Phase: Phase I (Bioequivalence)

Principal Investigator and Clinical Unit: [redacted]

Subject study number: *<leave blank>* | Study period: *<leave blank>*

Treatment: T | Batch no.:

Retest date:

Route of administration: Oral (with 240 mL of still water)

Manufacturer: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

Storage conditions: In the original primary package not exceeding 25° C

Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

Sample REFERENCE:

*Sample medication details to be checked*

*INVESTIGATIONAL DRUG FOR CLINICAL STUDY USE ONLY*

Global CRO: Anapharm Europe, S.L.U. [redacted]

ARCOXIA® 120 mg film-coated tablets (R)

Dosage: 1 film-coated tablet

Clinical Study Code: 20ANE-3489C

Phase: Phase I (Bioequivalence)

Principal Investigator and Clinical Unit: [redacted]

Subject study number: *<leave blank>* Study period: *<leave blank>*

Treatment: R Batch no.:

Expiry date:

Route of administration: Oral (with 240 mL of still water)

Manufacturer: Merck Sharp & Dohme B.V., the Netherlands

Storage conditions: In the original package in order to protect from moisture

Sponsor: PrJSC "Pharmaceutical firm "Darnitsa", Ukraine

## *11. CLINICAL PROCEDURES*

Unless otherwise stated in this protocol, the CU SOPs on the conduct of clinical procedures must be followed. A summary of the clinical assessments to be conducted over the course of the trial is presented in Table 1:

## 11.1. Study Plan

**Table 1.** Study Flow Chart

| **Study Period** | **SCR** | | | | | **Period 1** | | | | | **Washout[a]** | **Period 2** | | | | | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-5** | **-4** | **-3** | **-2** | **-1** | **-1** | **1** | **2** | **3** | **4** | **-10 to -2** | **-1** | **1** | **2** | **3** | **4** | **[c]** |
| **Procedures** | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demographic data (gender, race, age) | X | | | | | | | | | | | | | | | | |
| Demographic data (height, weight and BMI) | | | X | | | | | | | | | | | | | | |
| Medical, surgical history and previous medication check | X | | | | | | | | | | | | | | | | |
| Physical examination | | | X | | | | | | | | | | | | | | X |
| Inclusion / Exclusion criteria | X | | | | X | X | | | | | | X | | | | | |
| Forehead body temperature | X | X | X | X | X | | X | X | X | X | X[b] | X | X | X | X | X | X |
| Blood pressure / Heart rate | | | X | | | | X | | | | | X | X | | | | X |
| Urine drugs of abuse screen | | | | | X | | | | | | | | | | | | |
| Cotinine test | | | | | X | | | | | | | | | | | | |
| Breath alcohol test | | | | | X | | | | | | | | | | | | |
| COVID-19 RT-PCR Test | X | | | X | | | | | | | | | | | | | X[d] |
| 12-lead ECG | | | X | | | | | | | | | | | | | | X |
| Biochemistry / Haematology blood sampling | | | X | | | | | | | | | | | | | | X |
| Serology blood sampling | | | X | | | | | | | | | | | | | | |
| Urinalysis | | | X | | | | | | | | | | | | | | X |
| Meals | | | | | | X | X | | | | | X | X | | | | |
| Study Drug administration | | | | | | | X | | | | | | X | | | | |
| 200 mL of water | | | | | | | X | | | | | | X | | | | |
| Pk blood sampling | | | | | | | X | X | X | X | | | X | X | X | X | |

| | | |
|---|---|---|
| General health, adverse events and other medications check | X → X | |
| Isolation period at the hotel | X → X | |
| Confinement at the Clinical Unit | | X → X |

[a] *At least 14 days between each dosing*
[b] *Forehead body temperature will be measured each day of washout period*
[c] *Follow up visit will be performed before subject's leave the CU after the last PK blood sample in Period 2 has been collected for each subject*
[d] *To be performed the day before subject's discharge from the CU.*

## 11.2. Screening

Before any screening activities are performed, subjects will sign and date the study ICF and Subject Information Sheet (SIS), except for forehead body temperature. Forehead body temperature will be measured on Day -5 before ICF and SIS signature but it won't be registered on subject's CRF.

The screening will be carried out within 5 days prior to Day 1 Period 1.

On Day -5 subjects will attend to the CU and the study assessments indicated on Table 1 will be performed, including the first COVID-19 RT-PCR Test and the second forehead body temperature measurement. After these first assessments, subjects will be confined under supervision of the CU staff during five days in single rooms in a hotel near to the [redacted]. Movements between the CU and the hotel will be on foot. Forehead body temperature will be measured again on Day -4 at the hotel. Subjects will return to the CU on Day -3 to perform the screening assessments indicated on Table 1. A second COVID-19 RT-PCR Test will be performed on Day -2 at the CU along with forehead body temperature measurement and subjects will return for isolation to the hotel until second COVID-19 RT-PCR Test is negative confirmed. After that, subjects will be admitted to CU on Day -1 to perform the rest of screening assessments indicated on Table 1. In case of positive result for any COVID-19 RT-PCR test, it will be notified to Turkish Ministry of Health for further safety actions out of the study's scope.

Clinical staff will ensure that all scheduled clinical procedures are conducted and appropriately recorded in the CRFs during screening. To ensure subject's suitability prior to inclusion in the study, clinical staff will perform CRF checks to ensure subjects fulfil the eligibility criteria stated in Section 8.

Clinical assessments to be performed at the screening visit are presented below:

### 11.2.1. Demographic Data

Individual subject demographics (age, gender, race, weight, height and BMI) will be recorded.

### 11.2.2. Medical and Surgical History

Personal, family allergy and/or disease history will be recorded as well as surgical history.

### 11.2.3. Participation in Other Clinical Studies and Blood Donation History

Details on the last subject's participation in a clinical trial and blood/plasma donation will be recorded.

### 11.2.4. Substance Use Habits

Alcohol and nicotine use will be recorded. History of drug abuse and use of illegal drugs will be recorded.

### 11.2.5. Previous Medication Check

Past and current intake of any medication will be recorded.

### 11.2.6. Physical Examination

Physical examination will involve an assessment of the following systems: skin, head, neck, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, hepatic, biliary, endocrine, metabolic, lymph nodes, urogenital, neurological, psychiatric, musculoskeletal and other, if any.

### 11.2.7. Vital Signs

Blood pressure (BP: SBP and DBP), HR and forehead body temperature will be measured. In cases where a subject shows an out of range result, repeat measurements may be made at the Investigator's discretion.

### 11.2.8. Clinical Laboratory

Biochemistry, haematology and serology blood samples will be collected. A urine sample will be taken to perform urinalysis.

Clinical laboratory parameters are presented in Table 2:

**Table 2.** Laboratory parameters

| Biochemistry | Haematology | Serology | Urinalysis |
|---|---|---|---|
| Glucose (fasting) | Erythrocytes | HBsAg | pH |
| Creatinine | Haemoglobin | HIV-Ab | Specific Gravity |
| BUN | Haematocrit | Anti-HCV | Protein |
| Bilirubin | Leukocytes | | Glucose |
| Aspartate transaminase (AST) | Platelet count | | Urobilinogen |
| Alanine transaminase (ALT) | | | Bilirubin |
| Gamma-GT | | | Leukocytes |
| Alkaline Phosphatase | | | Nitrites |
| Potassium | | | Ketones |
| Sodium | | | Blood |
| Chloride | | | Microscopic examination of sediment |
| Uric acid | | | |
| Protein, total | | | |
| Calcium | | | |

The Investigator will assess the clinical relevance of each out-of-range laboratory result. Values outside the reference limits which are suspected to be of any clinical relevance may be repeated at the Investigator's discretion. Subjects with confirmed clinically relevant values upon repeated sampling will not be included in the study.

### 11.2.9. 12-lead ECG

A Research Physician will review all recorded ECGs and will document clinical evaluations in the CRFs. Should a subject show an abnormal ECG deemed clinically relevant, additional ECG measurements may be performed at the Investigator's discretion.

#### 11.2.10. Other Tests

Breath alcohol test will be performed.

Urine will be tested for cotinine and drugs of abuse. The following drugs of abuse will be screened: Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates.

Subjects who fail any of the above tests will be not included in the study.

#### 11.2.11.COVID-19 RT-PCR Test

COVID-19 RT-PCR Test will be performed on Day -5 and Day -2 of screening. If a subject is positive for COVID-19 on RT-PCR Test, they will be not included in the study.

#### 11.2.12. Standby Subjects

Sufficient number of standby subjects should be recruited to replace subjects who drop-out or are withdrawn from the study before first dosing. Standby subjects will undergo all admission and pre-dose procedures in Period 1 and will remain in the CU until dosing procedures are completed for all subjects on Day 1 Period 1.

Standby subjects replacing any volunteer will keep their original standby number (e.g. S001), which will be used to identify them throughout the study.

In case of replacement, standby subjects will receive the study medication that was labelled using the study subject number of the drop-out volunteer (e.g. 006) they are replacing.

In case of replacement, the "Study Termination" CRF page of the drop-out volunteer will be completed immediately.

### 11.3. Study Periods

In the evening of Day -1, the CU will receive the remaining screening results, including the results of the second COVID-19 RT-PCR Test. If subjects are eligible to continue in the study, they will be in confinement in the CU until the FU visit which will be performed before the subject leaves the CU after the last PK blood sample in Period 2 has been collected.

Assessments to be performed throughout the study are described below:

#### 11.3.1. Admission to the Clinical Unit and Pre-dose Procedures

In Day -1 Period 1, subject's identity and luggage will be checked at admission. A subject study number (i.e. randomisation number) will be allocated to each volunteer according to the order of admission to the CU.

Eligibility of subjects (i.e. inclusion/exclusion criteria and restrictions) will be re-evaluated upon admission based on the assessments specified on Section 11.2, due to the last day of screening assessments (Day -1) is the same calendar day that the admission day to the Clinical Unit in Period 1. Subjects will receive a standardised light dinner scheduled to end at least 10 hours prior to drug administration on Day 1.

On Day -1 Period 2, vital signs (BP, HR and forehead body temperature) will be measured for all volunteers.

After a supervised overnight fast, pre-dose vital signs (BP, HR and forehead body temperature) will be measured for all volunteers. Subjects will not be allowed to drink fluids within 1 hour pre-dose aside from 240 mL of still water to be provided upon dosing. Discontinuation criteria will be checked for all subjects prior to dosing.

Pk blood samples will be collected before dosing in each study period.

Admission and pre-dose procedures as described above will also be performed for standby subjects in Period 1.

### 11.3.2. Study Drug Administration

The identity, integrity and appearance of study medications will be checked against the corresponding certificate of analysis or SmPC prior to each administration.

Subjects will receive an oral dose of either Test or Reference product in the morning of Day 1 under a fasted state of at least 10 hours according to the study randomisation list. Administration will be performed with 240 mL of still water at ambient temperature. Subjects will be dosed consecutively at specific time intervals as deemed appropriate by the Investigator to allow for an accurate pk sample collection.

Upon dosing, study medication must be swallowed whole and must not be chewed or broken. Subject's hands and mouth will be checked using a torch and a disposable spatula to confirm the medication has been taken appropriately.

The actual time of administration will be recorded immediately after dosing and the tear-off segment of the IMP label will be placed on the relevant CRF page.

Standby volunteers who were not used to replace drop-outs/withdrawals prior to dosing in Period 1 will be discharged from the unit after dosing procedures have been completed.

Subjects will receive IMP at the same time in each study period.

The Investigator will supervise the study drug administration procedure.

#### 11.3.2.1. Study Drug Accountability

The CU will handle the study drug in their premises in accordance with their internal SOPs. Records of receipt, storage, movements, dispensing, dosing and final accountability will be maintained in relevant study forms by designated staff. Drug accountability records will be made available to the Sponsor or designee when requested.

Study drugs must not be used for any purpose other than the present study.

A final reconciliation of all study drugs will be performed upon completion of the study. The Sponsor may arrange for the remaining medication (T and R) and all empty medication containers to be shipped back, or may request that the Investigator handles destruction.

#### 11.3.2.2. Treatment Compliance

Measures to ensure treatment compliance and recording of treatment compliance will include:

- The Investigator will supervise study drug administration for all subjects.
- Subject's mouth and hands will be checked after dosing.
- Dosing procedures will be recorded on the relevant CRF page immediately after administration.
- Study drug accountability forms will be maintained and reviewed by designated staff during the study.

### 11.3.3. Post-dose Procedures

The Investigator will be present at the CU for at least 4 hours post-dose in both study periods and will remain on call at all times for the entire duration of the study.

Pk blood samples will be collected as stated in Section 14.1.

200 mL of still water will be provided at 2 hours post-dose. Subjects will be allowed to drink still water *ad libitum* from 4 hours post-dose.

On each dosing day, vital signs (SBP, DBP and HR) will be measured at 1, 6 and 12 hours post-dose, while forehead body temperature will be measured at 12 hours post-dose only.

A standard lunch and dinner will be served at 4 and 10 hours post-dose, respectively.

Subjects will be asked about their health and occurrence of AEs at the following timepoints in each period: Day -1, Day 1 (pre-dose, 1h, 5h and 12h post-dose), Day 2 (24h and 36h post-dose), Day 3 (48h post-dose) and Day 4 (72h post-dose).

In each study period, forehead body temperature will be measured on Day 2, Day 3 and Day 4.

Subjects will be discharged from the CU after the assessments of the FU visit have been performed. However, if judged necessary by the Investigator or delegate, subjects might be advised to stay in the CU for a longer period of time for safety reasons.

## 11.4. Follow up Visit

The end-of-study procedures (i.e. FU procedures) will be performed before the subject leaves the Clinical Unit (CU) after the last PK blood sample in Period 2 has been collected.

For subjects who received at least one dose of study medication and whose participation in the study is discontinued prior to the FU visit, the scheduled FU procedures (Early Termination (ET)) will be performed before the subject leaves the CU after the last study drug administration.

The following clinical procedures will be performed at the FU visit:

- **Physical examination**: Refer to Section 11.2.6 for details on the systems to be examined.
- **Vital signs**: BP, HR and forehead body temperature will be recorded.
- **ECG**: A 12-lead ECG will be performed.

- **Clinical laboratory tests**: Biochemistry, haematology tests and urinalysis will be performed.
- **COVID-19 RT-PCR Test:** A third COVID-19 RT-PCR Test will be performed the day before subject's discharge from the CU.

The Investigator will assess the clinical relevance of each abnormal result for the above tests.

## *12. STUDY TERMINATION*

Study termination (clinical phase) is defined as the LSLV of the study.

### 12.1. Premature Study Termination

The Sponsor may terminate the study at any time for scientific or strategic reasons.

The Investigator has the right to terminate the study prematurely for safety reasons after informing and consulting the Sponsor.

In case of premature termination of the study, the Investigator must document the reasons for termination and will perform the scheduled FU/ET procedures for all enrolled subjects. The Independent Ethics Committee (IEC) and Regulatory Authority will be informed when required.

## *13. ADVERSE EVENTS*

### 13.1. Subject's Safety Monitoring

Clinical staff will be available for the entire duration of the study. Emergency equipment (incl. emergency medication) will be available in the CU throughout the study.

In case of an emergency situation that could not be solved at the CU, subjects will be brought to the Emergency Medicine Department of Erciyes University Hospital to receive appropriate medical care.

### 13.2. Definitions

**Adverse Event:** Any untoward medical occurrence (sign, symptom or laboratory finding) in a clinical investigation subject, who was administered an IMP that does not necessarily have a causal relationship with the IMP. An AE can therefore be any unfavourable and unintended sign (including a clinically relevant abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP, whether or not related to the IMP.

**Adverse Reaction (ADR)**: Noxious and unintended responses to an IMP which occur at any dose and a causal relationship between the IMP and AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

**Serious Adverse Event (SAE)**: Untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions);
- Is a congenital anomaly or birth defect;
- Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the investigator);
- Any suspected transmission of an infectious agent via a medicinal product.

### 13.3. Severity

The severity of an AE will be classed as follows by the Investigator:

- **Mild:** Causing no limitation of usual activities; the subject may experience slight discomfort.
- **Moderate:** Causing some limitation of usual activities; the subject may experience annoying discomfort.
- **Severe:** Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

### 13.4. Causality

The causality assessment of an AE to the IMP will be rated as follows by the Investigator:

- **Reasonably possible (related):** There are facts (evidence) or arguments to suggest a causal relationship between the AE and the IMP administered; may be a temporal relationship between the AE onset and the administration of the IMP that cannot be readily explained by the subject's clinical state or concomitant therapies; or that the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions; or the AE profile of the IMP (2). In case of cessation of the dose due to the occurrence of an AE, the AE may abate or resolve.
- **Not reasonably possible (not related):** Evidence exists that the AE has a different causality than the IMP.

### 13.5. Expectedness

An unexpected AE is any untoward medical occurrence whose nature, severity or outcome is not consistent with the relevant safety information of the Reference product.

All reported AEs will be classed as expected or unexpected by the Sponsor in accordance with the SmPC of the Reference medication. The expectedness of all study AEs will be presented in the CSR.

### 13.6. Adverse Event Collection

The period of observation for collection of AEs extends from the screening until the FU visit (incl. washout period) for each subject. Any AEs occurring within this period will be recorded in the CRF.

At least the below details in relation to AEs will be reported by the Investigator:

- Description of the event
- Onset of the event (date and time)
- End of the event (date and time)
- Seriousness
- Severity
- Relationship with study drug (causality assessment)
- Last study drug administered prior to AE occurrence (incl. date and time)
- Action taken
- Outcome

The Sponsor will code all reported AEs by System Organ Class (SOC) and Preferred Term (PT) using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA coding of all reported AEs will be included in the CSR. AEs occurring after the subject signs ICF but before the first administration of IMP will be reported separately from those occurred after the first IMP administration.

It is the Investigator's responsibility to ensure that subjects who experience any AE receive appropriate follow up and treatment when required. Every action taken as a consequence of an AE must be appropriately documented.

In cases where there is any open AE after the FU visit, every effort should be made to follow the AE to resolution, give a reasonable explanation for its persistence, or to report it is mild and safely resolving.

### 13.7. Notification of SAEs

SAEs arising during the period for collection of AEs as defined in Section 13.6 must be reported to the Sponsor, Anapharm Europe S.L.U. and to IDEAL CRO within 24 hours regardless of their relationship to study drug. SAEs will be notified using the *Form for Serious Adverse Events Reports* located in Appendix 21.3, which will be filled in English.

Additional details on any SAE that were not available at the time of the first notification should be reported within the next few days and no later than 24 hours after the information becomes available using a follow up *Form for Serious Adverse Events Reports* (Appendix 21.3).

Contact details from the parties to be informed in case of occurrence of a SAE are provided below:

Sponsor:

[redacted]
Qualified person responsible for pharmacovigilance
PrJSC "Pharmaceutical firm "Darnitsa"
02093, 13, Boryspilska str., Kyiv, Ukraine
[redacted]

Global CRO: [redacted]
Clinical Services Director
Anapharm Europe, S.L.U.
[redacted]

Local CRO: [redacted]
Technical Manager
IDEAL Biyolojik Ürünler ve İlaç Danışmanlık Eğitim Ltd. Şti./Pharma Consulting (IDEAL CRO)
[redacted]

In accordance with local legislation (4), all Suspected Unexpected Serious Adverse Reactions (SUSARs) and SAEs will be notified to the IEC and the local Regulatory Authorities. This notification will be made by IDEAL CRO. Timelines for notification will be as follows:

- Fatal or life-threatening SUSAR will be reported as soon as possible and no later than 7 calendar days after IDEAL CRO awareness of the minimum criteria for reporting (i.e. adverse reaction assessed as serious and unexpected, identifiable subject, suspected IMP and identifiable reporting source). Relevant FU information should be communicated within 8 days after the first SUSAR report has been emitted.
- Non-fatal or non life-threatening SUSAR, will be reported as soon as possible and no later than 15 calendar days after IDEAL CRO awareness of the minimum criteria for reporting.

Reporting of SAEs to the relevant international and/or local regulatory authorities where the Sponsor is based will be performed by the Sponsor when required.

## *14. BIOANALYSIS ASSESSMENTS*

### 14.1. Pk Blood Samples

A total of 20 blood samples of 4 mL will be collected in each study period in EDTA $K_2$ tubes for the determination of etoricoxib. Pk samples will be collected from an indwelling cannula placed in the forearm vein of the subject whenever possible. If judged necessary by the CU staff, direct venepuncture might be used. Blood sample tubes will be labelled with at least the details below:

- Clinical study code
- Subject study number / Standby number
- Study period

- Sample no.

The pk sampling schedule of each study period is presented in Table 3:

**Table 3.** Pk sampling schedule

| Sample No. | Sampling Time [h] |
|---|---|
| 01 | 0.000 (Pre-dose) |
| 02 | 0.083 |
| 03 | 0.167 |
| 04 | 0.250 |
| 05 | 0.333 |
| 06 | 0.500 |
| 07 | 0.750 |
| 08 | 1.000 |
| 09 | 1.250 |
| 10 | 1.500 |
| 11 | 2.000 |
| 12 | 3.000 |
| 13 | 4.000 |
| 14 | 6.000 |
| 15 | 8.000 |
| 16 | 12.000 |
| 17 | 24.000 |
| 18 | 36.000 |
| 19 | 48.000 |
| 20 | 72.000 |

Pk sampling times will be set in accordance with the dosing schedule. Actual blood collection times will be recorded on the relevant CRF pages immediately after each blood draw for each subject. All deviations from the scheduled sampling time (Table 3) will be considered protocol deviations and will be reported in the CSR. Unless otherwise stated or due to safety reasons, in cases where a pk blood draw overlaps with other clinical procedures, pk blood collection will take priority.

## 14.2. Volume of Blood Sampling

The maximum blood volume planned to be collected per subject will not exceed 195 mL (160 mL for pk and 35 mL for clinical laboratory sampling).

Blood will be obtained in small volumes over several days and it is not anticipated to pose any risk to subjects or to affect the pk profiles of the study drugs (and hence the assessment of BE).

The total volume of blood drawn per subject may be slightly higher if repeated samples are collected for safety reasons.

### 14.3. Pk Sample Processing, Storage and Shipping

Pk samples will be processed, stored and shipped to the bioanalytical laboratory as stated in the Analytical Methodology Information Sheet (AMIS). Sample handling procedures will be appropriately documented.

Two plasma aliquots will be created for each timepoint. Pk sample labels will contain at least the details below:

- Clinical study code
- Subject study number / Standby number
- Study period
- Sample no.
- Aliquot identification

Any sample movements between freezers in the CU will be registered. Temperature of freezers containing study samples will be continuously monitored and recorded.

Pk samples will be shipped in thermo-isolated boxes containing dry ice. The first and second batch of plasma aliquots will be sent in two separate shipments. The second batch will only be shipped once the bioanalytical laboratory confirms the first batch has been received. Temperatures of pk sample transport will be recorded using a data logger.

The bioanalytical laboratory will continuously monitor and record temperatures of freezers containing study samples.

### 14.4. Bioanalytical Assay

All pk blood samples obtained from all dosed subjects will be assayed.

Etoricoxib plasma concentrations will be determined using a validated bioanalytical LC/MS/MS method in compliance with the applicable EMA regulations (5) and GLP.

The Bioanalytical Protocol must be signed off prior to the start of pk sample analysis. A Bioanalytical Report will be issued to the Sponsor by the bioanalytical laboratory after completion of bioanalysis.

The bioanalytical laboratory staff will not have access to the study randomisation list.

No pk sample analysis will be repeated due to pk reasons.

In order to establish the reproducibility of the assay, incurred samples assessment will be performed according to applicable EMA regulations (5).

Bioanalytical sample analysis will only start after the last study pk sample has been collected.

# 15. PHARMACOKINETICS AND STATISTICAL ANALYSIS

## 15.1. Sample Size

Based on published data (6) (7) (8) (9), the highest intra-subject Coefficient of Variation (CV) following an oral single dose of etoricoxib 120 mg appears to be approximately 20% for $C_{max}$. Taking into account this value and assuming the a priori maximum difference of 5% between formulations, according to the approach of Zhang P (10) it is estimated that a sample size of 26 subjects in a two-period, two-sequence design should be sufficient to meet the BE range with a statistical a priori power of at least 90% with an alpha level protection of 0.05. Therefore, the inclusion of 28 subjects should be sufficient to also cover any potential drop-outs/withdrawals and variations around the estimated intra-subject CV.

To ensure that 28 volunteers are administered with the study medication, at least 2 standby subjects will remain at the CU until the last subject is dosed in the first study period.

## 15.2. Pharmacokinetic Analysis

Etoricoxib plasma concentrations achieved by administering a single dose of study medication (T or R) will be measured to determine the pharmacokinetic profile of the Test product in relation to the Reference product.

The pk parameters that will be estimated are listed below:

- **$C_{max}$**: Maximum observed plasma concentration, obtained directly from the data – without interpolation.
- **$AUC_{0-72h}$**: Area under the plasma concentration time curve calculated from 0 to 72 hours, using the mixed model linear log trapezoidal rule. If there are concentrations below LLOQ (Lower Limit of Quantification) at 72 hours post-dose in at least one subject, then $AUC_{0-t}$ will be calculated for all volunteers instead of $AUC_{0-72h}$.*
- **$t_{max}$**: Time of maximum observed plasma concentration; obtained directly from the data – without interpolation. If this occurs at more than one time point, $t_{max}$ is defined as the first time point with this value.

* The following PK parameters will be calculated only in the event that not all subjects have quantifiable concentration levels at 72 hours post-dose (in addition to $C_{max}$ and $t_{max}$):

- **$AUC_{0-t}$**: Area under the plasma concentration time curve calculated from 0 to the last observed concentration above the LLOQ, using the mixed model linear log trapezoidal rule.
- **$AUC_{0-\infty}$**: Area under the plasma concentration time curve extrapolated to infinity.
- **Residual area (AUC%extra)**: Extrapolated area calculated as follows: ($AUC_{0-\infty}$ – $AUC_{0-t}$) / $AUC_{0-\infty}$ * 100.
- **$k_{el}$**: Elimination rate constant.
- **$t_{1/2}$**: Plasma half-life, calculated as $0.693/k_{el}$.

The actual sampling times (i.e. times at which the planned samples were actually collected) will be used for the calculation of pk parameters except for pre-dose samples, which will be reported as zero.

In cases where concentrations of etoricoxib cannot be determined due to bioanalytical or clinical reasons, these values will be set to missing (no value) for the pk analysis.

Below LLOQ concentrations will be treated as zero for all statistical analyses.

Data from subjects who provide evaluable pk data for both Test and Reference products will be included in the pk and statistical analysis for bioequivalence determination. Subjects that are non-evaluable for a particular study period (or treatment in this case, as the study is a two-way crossover) are:

- Subjects with a pre-dose concentration greater than the 5% of the $C_{max}$ value for the subject in that Period.
  (Note that if a pre-dose concentration of etoricoxib in Period 1 or 2 is detected but is equal to or less than 5% of the $C_{max}$ value for the subject in that Period, the subject's data will be included in the pk and statistical analyses without adjustment).
- Subjects presenting no measurable concentrations or only very low plasma concentrations for the Reference product (i.e. $AUC_{0-72h}$ (or $AUC_{0-t}$ if applicable) is less than 5% of the Reference product geometric mean $AUC_{0-72h}$ (or $AUC_{0-t}$ if applicable), which should be calculated without inclusion of data from the outlying subject): These subjects will be excluded from the pk and statistical evaluation. However, an additional statistical evaluation including such subjects will be performed and presented in the Statistical Report.
- Subjects who experienced any circumstance(s) that could imply that the plasma concentration-time profile is unreliable (i.e. due to AEs, concomitant medications, violation of study restrictions, missing pk samples): In these cases, decisions on the non-inclusion of these subjects in the pk and statistical analysis will be made by the Sponsor prior to the start of the bioanalysis. In case of missing pk samples, subjects will be only excluded from both pk and statistical analysis when there are more than 2 consecutive missing samples along the concentration-time profile. However, a sensitive analysis (bioequivalence assessment) will be performed including these subjects.

Although not included in the statistical BE assessment, pk parameters of non-evaluable subjects as per criteria mentioned above will be calculated if enough data are available and will be presented separately.

Samples from drop-out/withdrawal subjects will be assayed; however, subjects who do not provide evaluable data for both Test and Reference products (according to the above mentioned criteria), will not be included in the statistical analyses for BE determination and will be presented separately. If there are enough data available, pk parameters will be calculated for these subjects and will be presented separately.

The main PK parameters of interest for this study will be $C_{max}$ and $AUC_{0-72h}$. $t_{max}$ will be provided for information purposes only.

In case of not all subjects have quantifiable concentration levels at 72 hours post-dose, the main PK parameters of interest for this study will be $C_{max}$ and $AUC_{0-t}$. Other parameters such as $AUC_{0-\infty}$, residual area, $t_{max}$, $k_{el}$ and $t_{1/2}$ will be provided for information purposes only.

Pk parameters will be estimated using a non-compartmental approach with a log-linear terminal phase assumption.

Any decision for excluding data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

The mixed model linear log trapezoidal rule will be used to estimate the area under the curve and the terminal phase will be estimated by maximizing the coefficient of determination estimated from the log-linear regression model (using at least three available above LLOQ concentration points occurring after $C_{max}$ for the estimation of the $k_{el}$).

The individual etoricoxib concentrations as well as the actual sampling times will be listed for each subject, product and scheduled sampling time. Descriptive statistics will be tabulated.

Individual pk parameters will be listed by product and descriptive statistics will be calculated.

The individual plasma concentration/time profiles (linear and semi-log scales) will be presented using the actual sampling times whereas the mean plasma concentration/time profiles (linear and semi-log scales) will be presented using the theoretical sampling times by treatment. Individual plasma concentrations per treatment will be presented as spaghetti plots.

The determination of pk parameters will be carried out using the validated pharmacokinetic software Phoenix® WinNonLin® (v8.2 or an upgraded version) (11).

### 15.3. Statistical Analysis

Individual ratios (T/R) of $C_{max}$ and $AUC_{0-72h}$ will also be presented as part of the descriptive analysis. In case of not all subjects have quantifiable concentration levels at 72 hours post-dose, individual ratios (T/R) of $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ will also be presented as part of the descriptive analysis.

In any case, the natural logarithmic transformation of $C_{max}$, $AUC_{0-72h}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ will be used for all statistical inference.

$C_{max}$ and $AUC_{0-72h}$ (or $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ if applicable) will be statistically analysed using an ANOVA model. The fixed factors included in this model will be the subject effect (nested within sequence), the treatment received, the period at which it was given, as well as the sequence in which each treatment is received. In case of any significant effect by period or sequence, the magnitude of the effect will be calculated in terms of the ratio of both levels, using geometric means. Explanations for significant effects will be provided.

The 90% CI for the exponential of the difference in LSmeans between the Test and Reference product will be calculated for the ln-transformed $C_{max}$ and $AUC_{0-72h}$ parameters (or $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ if applicable) (Test to Reference ratio of geometric LSmeans).

The formula to estimate the intra-subject CV will be: CV(%)= 100 x $\sqrt{e^{MSE}-1}$, where MSE is the Mean Square Error obtained from the ANOVA model of the ln-transformed parameters.

In the event that the study is conducted in two or more groups and those groups are dosed at the same CU but greatly separated in time (1 month or more), the statistical model will be modified accordingly to incorporate the group effect. The fixed factors included in the modified model will be the study group, the treatment received, the period at which it was given, the sequence in which each treatment is received and the subject effect (nested within the group-by-sequence interaction).

Test vs Reference $t_{max}$ comparison will be performed, as an exploratory analysis, by means of the same ANOVA model but with a previous rank-transformation of un-transformed data.

The level of significance will be set to the standard value of 5% (0.05) for all statistical tests.

Statistical analyses will be generated using the Statistical Analysis System (SAS®) (3) (release 9.4 or an upgraded version) using the GLM method.

### 15.4. Criteria for Bioequivalence

The ratio of geometric LSmeans with corresponding 90% CI calculated from the exponential of the difference between the Test and Reference products for the ln-transformed parameters $C_{max}$ and $AUC_{0-72h}$ should both be within the acceptance interval of 80.00 - 125.00%.

In case of not all subjects have quantifiable concentration levels at 72 hours post-dose, the ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference products for the ln-transformed parameters $C_{max}$ and $AUC_{0-t}$ should be within the acceptance interval of 80.00 – 125.00%.

## *16. DATA MANAGEMENT*

Subjects who drop-out or are withdrawn before receiving the first study medication will not be included in either safety or pk analyses.

### 16.1. Pk Data Management

Pk data management and analyses will follow both Global CRO [redacted] and procedures described in Section 15.

A Statistical Analysis Plan and a Statistical Report will be generated for this study.

### 16.2. Safety Data

The safety population will include subjects who received at least one of the study medications.

Safety and tolerability assessments will be based on the descriptive statistical evaluation of the following safety parameters: Adverse events, safety laboratory parameters (biochemistry, haematology, serology and urinalysis), COVID-19 RT-PCR and vital signs (blood pressure (BP), HR and forehead body temperature).

ECG, physical examination, drugs of abuse, cotinine and alcohol test results will be listed.

At least, the below listings will be presented in the CSR:

- Demographic data
- Medical, Surgical history and Previous medication check
- Substance use habits
- Concomitant medications
- Physical examination
- Vital signs
- ECG
- Clinical laboratory tests
- Alcohol, cotinine and drugs of abuse tests
- COVID-19 RT-PCR Tests
- Adverse events

For consistency on the selection of safety data for descriptive statistical evaluation upon repeated measurements, the following criteria will apply:

- Repeats performed before study drug administration: the last observed value will be included in descriptive statistics.
- Repeats performed after study drug administration: the first observed value will be included in descriptive statistics.

Safety data management and analyses will follow the Global CRO SOPs.

### 16.3. CRF and Source Data

Paper CRFs will be designed to collect all required study data and will include instructions on how to record and amend the information correctly. CRFs will also state which data are considered to be source data.

The PI (or delegate) will be responsible for the completeness and accuracy of the information contained in the CRFs. Data will be recorded so that it is legible and in compliance with GCP. All CRF pages will be signed and dated by the PI or delegate.

At the end of the study, the original CRFs will be filed in the IF as some CRF sections are source document, while a final copy will be also shared with the Sponsor along with the study reports.

### 16.4. Quality Control and Quality Assurance

Designated staff from the Global CRO, CU, Bioanalytical Laboratory and Statistics Facility will be responsible for the QC and Quality Assurance activities (including audits) to ensure the study is

conducted and the data obtained, reported and documented in compliance with the CSP, ICH Guideline E6 for GCP, OECD Principles on GLP and the Reflection paper for laboratories involved in the analysis/assessment of clinical trial samples (EMA/INS/GCP/532137/2010).

Audit certificates will be included in the CSR as an Appendix.

### 16.5. Monitoring

A CSM will be designated by the Sponsor. The CSM will visit the CU before, during and after the study to maintain current personal knowledge of the study conduct by reviewing study records and source documents, observing and discussing any relevant study-related topic with the Investigator or delegated staff to ensure that the study is being conducted according to the CSP and GCP.

The CSM will write Monitoring Reports for each visit performed and will complete the corresponding study visit log.

Further details on monitoring for the study will be described in the corresponding Clinical Monitoring Plan.

### 16.6. Investigator's File

The PI (or delegate) will file all essential study documents in the Investigator's File (IF) in compliance with GCP. The IF will be stored at the CU premises.

### 16.7. Sponsor's Trial Master File

The Sponsor will file all essential study documents in the Sponsor's Trial Master File (TMF) in compliance with GCP. The TMF will be stored at the Sponsor's premises.

## *17. AMENDMENTS AND DEVIATIONS*

If any amendments to the CSP or ICF/SIS are to be made, all changes must be agreed between the CU, Sponsor, Global CRO, Project Statistician and Local CRO beforehand. The Investigator should not implement any amendments to the CSP without prior agreement between the abovementioned parties and before the approval from the IEC and/or the Regulatory Authority (in case of substantial amendments) has been granted, except where the change is necessary to eliminate immediate hazard(s) to study subjects.

Amendments will be documented and submitted to the relevant IEC and/or Regulatory Authorities for approval in accordance with applicable local regulations. Non-substantial amendments will be notified to the relevant authorities when required.

Time windows to perform scheduled post-dose clinical procedures are provided in Appendix 21.4. Procedures performed outside these windows will be considered protocol deviations and will be reported in the CSR.

Any deviation from the CSP will be recorded and explained.

# 18. CLINICAL STUDY REPORT

All study data, including pk (presented in the Appendices of the Statistical Report included as an Appendix of the CSR) will be reported in the CSR. Bioanalytical data will be presented in the Appendices of the Bioanalytical Report, not included in the CSR. The PI, Sponsor's representative, Statistician and Global CRO representative will sign the CSR to confirm agreement with its content.

Data contained in the CSR will be reported in accordance with the ICH (E3) (12).

# 19. REGULATORY REQUIREMENTS

## 19.1. Clinical Trial Application, Regulatory Authority and Independent Ethics Committee

A Clinical Trial Application (CTA) with all relevant supporting documentation must be submitted to the Regulatory Authority (The Turkish Medicines and Medical Devices Agency of the MoH) and the IEC (Ethics Committee for Bioavailability-Bioequivalence Trials of Erciyes University) according to local procedures in order to obtain all approvals/authorisations prior to the start of subject screening.

This study will be conducted in accordance with the following regulations:

- Guideline for GCP E6 (R2), Step 5, EMA/CHMP/ICH/135/1995), 1 December 2016 (13).
- Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**, London, 20 January 2010 (1).
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use (14).
- All applicable European Community laws, in particular Directives No. 2001/20/EC, 2005/28/EC and 2001/83/EC,
- Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010), 28 February 2012 (15).
- Declaration of Helsinki currently in force.
- ICH Topic E3: Structure and Content of CSRs, Step 5, Note for Guidance on Structure and Content of CSRs (CPMP/ICH/137/95), July 1996 (12).
- OECD Principles on GLP.
- Turkish Pharmaceutical and Medical Preparations Law No: 1262 (Publication Date in the Official Gazette: 26th May, 1928 Issue No. 898) (16).
- Turkish Regulation on Evaluation of Bioavailability and Bioequivalence of Pharmaceutical Products (1994) (17).
- Turkish Good Clinical Practice Guideline (13th November 2015) (18).
- Turkish Regulations Regarding Clinical Trials of Drugs and Biologics (Off. Gazette No: 28617, 13th April 2013, Amendment to the Regulation Off. Gazette No: 29041, 26th June 2014 and Off. Gazette No: 29474, 13th September 2015 (4).

- Other laws and regulations in force in the country where the study is conducted.

## 19.2. ICF and Subject Information Sheet

The informed consent is a process by which a subject voluntarily confirms his/her willingness to participate in a clinical study. It is the responsibility of the PI or delegate to obtain written informed consent from subjects prior to any screening procedures are carried out.

All potential participants will be given a full explanation of what the study involves, including but not limited to: the objectives, the procedures to be carried out, potential risks and subject's rights and responsibilities. After this explanation and before entering the study, subjects will be given enough time to read and voluntarily sign and date the study ICF/SIS. The document must be also signed and dated by the PI or delegate upon consent. Subjects will receive a signed copy of the ICF/SIS after consent.

Signed ICFs must remain in the CU premises and must be available for verification by the CSM at any time.

The IEC must approve any updated versions of the ICF and SIS prior to implementation.

Re-consent of enrolled subjects who have not yet completed the FU visit must be obtained if any amended version of the ICF/SIS is issued during the study.

## 19.3. Confidentiality

All parties involved in the study will preserve the confidentiality of all study subjects in accordance with GCP and applicable local regulations.

As some study procedures are performed in European Union sites, the Sponsor and CRO will observe the rules laid down in the Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and the free movement of such data of the European Parliament and of the Council of 27$^{th}$ April 2016.

The Investigator will permit authorised representatives of the Sponsor, CSM, Global/Local CRO, Regulatory Authority and the IEC direct access to the subject's original medical records for verification of study-related procedures and study data. The Investigator will make study subjects aware that the above aforementioned representatives will review their study-related records without breaching confidentiality.

## 19.4. Insurance

It is the Sponsor's responsibility to ensure that a suitable insurance cover is in place prior to the start of the study.

At least, an insurance policy certificate will be supplied to the CU prior to the start of the study.

### 19.5. Delegation of Investigator's Responsibilities

It is the PI's responsibility to ensure that all CU personnel involved in the study are adequately qualified and are familiar with the protocol and any amendment that may arise during the study, the study medications and their study-related duties and functions.

The PI will maintain a list of Co-investigator(s) and other qualified persons to whom delegates significant study-related duties are delegated.

### 19.6. Inspections

Regulatory inspections of this study may be carried out by the Regulatory Authorities to confirm that study procedures have been appropriately followed, that GCP has been adhered to and that the collected and reported data are reliable. These audits/inspections can occur at any time during or after completion of the study. Should an audit or inspection occur, all parties involved in the study will allow the auditor/inspector direct access to all relevant documents and will allocate time for them and their staff to discuss any relevant findings or issues with the auditor/inspector.

### 19.7. Archiving

All parties involved in the study will archive the essential study documents and records for a period of 25 years after completion of the study in accordance with the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use (14).

### 19.8. Publication Policy

Any publication related to this study requires prior written authorisation from the Sponsor to be published.

## *20. REFERENCES*

1. Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). European Medicines Agency. [Online].; London 2010. Access on 18th December 2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.

2. SmPC of Arcoxia® 120 mg Film-coated Tablets. Electronic Medicines Compendium (EMC). [Online].; September 2019. Access on 18th December 2020. Available at: https://www.medicines.org.uk/emc/product/10618/smpc.

3. SAS version 9.4 software. SAS Institute Inc., Cary, NC. [Online] Access on 18th December 2020. Available at: https://www.sas.com/es_es/home.html.

4. Turkish Regulations Regarding Clinical Trials of Drugs and Biologics (Off. Gazette No: 28617, 13th April 2013, Amendment to the Regulation Off. Gazette No: 29041, 26th June 2014 and Off. Gazette No: 29474, 13th September 2015.

5. Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). European Medicines Agency. [Online].; London 2011. Access on 18th December 2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf.

6. Etoricoxib Alter 30 mg, 60 mg, 90 mg and 120 mg Film-Coated Tablets (ES/H/0411/001-004/DC). Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). [Online].; January 2017. Access on 18th December 2020. Available at: https://cima.aemps.es/cima/pdfs/ipe/81826/IPE_81826.pdf.

7. Etoricoxib Mylan 30 mg, 60 mg, 90 mg and 120 mg, film-coated tablets (NL/H/3196/001-004/DC). Heads of Medicines Agencies (HMA). [Online].; 2016. Access on 18th December 2020. Available at: https://mri.cts-mrp.eu/Human/Downloads/NL_H_3196_004_PAR.pdf.

8. Tjandrawinata R., et al. Pharmacokinetic equivalence study of nonsteroidal anti-inflammatory drug etoricoxib. Clinical Pharmacology: Advances and Applications. 2018;(10): p. 43-51.

9. Najib O., et al. Bioequivalence Evaluation of Two Brands of Etoricoxib 120mg Tablets (Etoricoxib-SAJA & ARCOXIA®) – in Healthy Human Volunteers. Modern Clinical Medicine Research. 2017; 1(1).

10. Zhang P. A simple formula for sample size calculation in equivalence studies. J Biopharm Stat. 2003; 13(3): p. 529-538.

11. Phoenix® WinNonLin® v8.2. Certara. Pharsight Corporation. [Online] Access on 18th December 2020. Available at: https://www.certara.com/.

12. Structure and Content of Clinical Study Reports (CPMP/ICH/137/95). European Medicines Agency. [Online]; London 1996. Access on 18th December 2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-content-clinical-study-reports-step-5_en.pdf.

13. Guideline for good clinical practice E6(R2) (EMA/CHMP/ICH/135/1995). European Medicines Agency. [Online].; London 2016. Access on 18th December 2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.

14. Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Comission. [Online].; 16th April 2014. Access on 18th December 2020. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

15. Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010). European Medicines Agency. [Online].; London 2012. Access on 18th December 2020. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-laboratories-perform-analysis-evaluation-clinical-trial-samples_en.pdf.

16. Turkish Pharmaceutical and Medical Preparations Law No: 1262 (Publication Date in the Official Gazette: 26th May 1928, Issue No. 898).

17. Turkish Regulation on Evaluation of Bioavailability and Bioequivalence of Pharmaceutical Products (1994).

18. Turkish Good Clinical Practice Guideline (13th November 2015).

## *21. APPENDICES*

# Appendix

## 21.1. Declaration of Helsinki

# WORLD MEDICAL ASSOCIATION

# DECLARATION OF HELSINKI

## Ethical Principles for Medical Research Involving Human Subjects

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

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, 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 authorised 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 authorised 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 authorised 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 authorised representative, may use an unproven intervention if in the physician's judgement 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

## 21.2. Informed Consent Form and Subject Information Sheet

# Informed Consent Form

**Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions**

**Clinical Study Code:** 20ANE-3489C

**Sponsor Study Code:** ETR01-E

**Date:** 23.DEC.20, **Final Version** 01

**IK No:** |_|_|_|_|_|_| **Screening No:** |_|_|_|_|

**Global CRO:**

Anapharm Europe, S.L.U.

**Sponsor:**

PrJSC "Pharmaceutical firm "Darnitsa"

**Principal Investigator (Reachable 24 hours a day)**

[redacted]

Erciyes University Hakan Çetinsaya

İyi Klinik Uygulama ve Araştırma Merkezi, IKUM (Center for GCP)

[redacted]

**This Informed Consent Form is for volunteers who attend Erciyes University Hakan Çetinsaya İyi Klinik Uygulama ve Araştırma Merkezi IKUM (Center for GCP), and whom we are inviting to participate in the research on the bioequivalence (interchangeability of the preparations in therapy) of Exib 120 mg etoricoxib film-coated tablets, manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine) in comparison with the reference product Arcoxia 120 mg etoricoxib film-coated tablets, manufactured by Merck Sharp&Dohme B.V. (The Netherlands) under fasting conditions.**

**This Informed Consent Form has two parts:**

- **Subject Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

**You will be given a copy of the full Informed Consent Form.**



Paraph of the Volunteer:

# *SUBJECT INFORMATION SHEET*

**Dear volunteer,**

The drug tested in the present trial is Exib 120 mg film-coated tablets (FCT), manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine), containing as active substance etoricoxib. Etoricoxib belongs to a group of medicines called selective cyclo-oxygenase-2 inhibitors that belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) and helps to reduce the pain and inflammation in the joints and muscles of people with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and gout. It is also used for the short term treatment of moderate pain after dental surgery. We invite 28 volunteers including you to participate in this study. This sheet is giving the information written which is also presented to you verbally. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. There may be some words that you do not understand. Please ask your questions to the physician who gives you this information during the information meeting. If you have questions later, you can ask them anytime.

## Purpose and Type of Research

The purpose of the present trial is to investigate the bioequivalence (interchangeability of the preparations in therapy) of an oral test preparation with an oral reference preparation, containing 120 mg of etoricoxib under fasting conditions. The reference drug is already registered in the European Union (EU) as Arcoxia 120 mg FCT. For the purpose of registration, the efficacy and safety of this drug were proven in clinical trials. This drug will therefore serve as reference and a basis for comparison for the test drug Exib 120 mg FCT containing 120 mg of etoricoxib, which is manufactured by PrJSC "Pharmaceutical firm "Darnitsa" (Ukraine).

## Time Period of the Study

You will be requested to come to the clinic for the screening visit (SCR), which will be carried out within 5 days before the beginning of the trial. During four nights you will remain isolated in a hotel [redacted]) near to the Clinical Unit under supervision of the clinical staff. The screening assessments will be performed at the Clinical Unit. Movements between the CU and the hotel will be on foot. If the laboratory and examination results are satisfying, you will remain in the Clinical Unit for approximately for 19 days and 18 nights. There will be at least a 14 days washout interval between the two drug administrations (namely two study periods). You will be given a total of 2 medications in two occasions. The sequence of drug intake will be randomly assigned within the trial. You have therefore equal chances of beginning with any of the drugs. The final follow up visit (FU) will be carried out before you leave the clinical unit after the last blood sample in Period 2 has been collected and the study will be completed. The total duration of the trial is approximately 23 days.

| **Study Period** | **SCR** | | | | | **Period 1** | | | | | **Washout** | **Period 2** | | | | | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-5** | **-4** | **-3** | **-2** | **-1** | **-1** | **1** | **2** | **3** | **4** | **-10 to -2** | **-1** | **1** | **2** | **3** | **4** | * |
| **Procedures** | | | | | | | | | | | | | | | | | |
| Study Drug administration | | | | | | | X | | | | | | X | | | | |
| Isolation period at the hotel | X → | | | | X | | | | | | | | | | | | |
| Confinement at the Clinical Unit | | | | | | X → | | | | | | | | | | | X |

** The final follow up (FU) visit will be carried out before you leave the clinical unit after the last blood sample in Period 2 has been collected.*

## Participant Selection

28 healthy male volunteers will participate in this study.



Paraph of the Volunteer:

## Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Additionally, you are free to withdraw from this clinical study at any time without giving reasons and without jeopardizing the further need of clinical treatment. Your signature under the Informed Consent Form does by no means oblige you to complete the study.

## Procedures and Protocol

The screening visit is carried out within 5 days before the beginning of the trial and includes standard clinical and laboratory screening and COVID-19 (Coronavirus disease-19) Tests. For COVID-19 tests a swab will be used to take a sample from throat and nose. As a standard safety procedure, on each admittance to the Clinical Unit, your body temperature will be measured. During four nights, you will remain isolated in a single room in a hotel [redacted] near to the Clinical Unit under supervision of the clinical staff. You will be under the supervision of a security personnel for 24 hours and during your entire stay at the hotel. Additional random controls will be made by the clinical staff. The hotel is monitored by a 24-hour video system. These records will be deleted 200 days after being recorded. Your body temperature will be measured during these five days. You will attend to the Clinical Unit to perform the screening assessments on Day -5, Day -3, Day -2 and Day -1. Movements between the CU and the hotel will be on foot. In the standard clinical screening, your age, gender, race, weight and height will be recorded and the physician will ask you about your past and current medical condition, any past surgeries and previous medication intake. The screening visit will also involve a complete physical examination, measurements of forehead body temperature, blood pressure and heart rate, a standard ECG (12 leads) (a method which records electrical potential changes in the heart) and a breath alcohol test. Blood samples of approximately 20 mL in total will have to be taken for standard laboratory screening tests, including Hepatitis and HIV tests. If necessary, some more blood may be taken for a control examination in case of any problems. All volunteers will be requested to provide a urine sample for standard laboratory assessments at screening. A drug (causing addiction) screen will also be performed on your urine which will include amphetamines, cannabinoids, benzodiazepines, cocaine, opioids and barbiturates. Cotinine will also be tested in your urine to verify that you have not smoked recently. Two COVID-19 Tests will be performed before admission to the Clinical Unit. The first COVID-19 test will be performed on Day-5 of screening, after that, volunteers will go to the hotel for isolation. The second COVID-19 test will be performed on Day-2 of screening, after that, volunteers will return to the hotel and in case of negative result, volunteers will be admitted to the Clinical Unit to continue with the rest of screening procedures. In case of positive result for COVID-19 test, you will not be able to participate in the study and it will be notified to Turkish Ministry of Health for further safety actions out of the study's scope.

If you are suitable for the study, you will remain in the Clinical Unit for 19 days and 18 nights (until the morning of Day 4 in Period 2). So the total time you will spend for this study in the hotel and the clinical unit will be 23 days.

On admission to the clinic, the luggage of all volunteers will be checked for not allowed items (food, beverages, cigarettes, chewing-gum and any drugs). A security service personnel will perform a security check on your body and your luggage by hand on admission to the clinic and before the start of confinement at the Clinical Unit.

An evening snack will be provided at approximately 7:30 pm on admission day. On Day -1 Period 2, vital signs (blood pressure, heart rate and forehead body temperature) will be also measured.

In this study, each one of the 28 volunteers will receive a single oral dose of the test (T) (containing 120 mg of etoricoxib) or a single oral dose of the reference drug (R) (containing 120 mg of etoricoxib) under fasting conditions in one occasion each.

On the day of dosing, blood pressure, heart rate and forehead body temperature measurements will be performed prior to dosing, which will commence at a designated time about 07:00 – 09:00 am. 1 film-coated tablet of the test preparation or 1 film-coated tablet of the reference preparation (containing 120 mg of etoricoxib in each case) will be swallowed with 240 mL of water while standing. This will be

followed by a mouth and hands check. You will be provided a standard lunch and a standard dinner at 4 and 10 hours after dosing, respectively.

You will abstain from food from 9:00 pm in the evening before dosing (minimum 10 hours) until lunch time on dosing day (approximately 4 hours post dose). You are not allowed to drink water other than that amount given for drug administration from one hour before to four hours after administration except for 200 mL of water that will be provided to you 2 hours after dosing; you may drink water the rest of the time.

The use of the toilet will be restricted for at least 4 hours after study drug administration.

Blood pressure and heart rate will be also measured at 1, 6 and 12 hours and forehead body temperature at 12 hours only following each dosing.

A final follow up visit will be performed the same day after your last PK blood sample collection on Period 2. This visit will involve the following clinical assessments: Physical examination, blood pressure, heart rate, body temperature measurements, a standard ECG (12 leads) and the third COVID-19 Test which will be performed the day before of your discharge from the CU. Blood samples of approximately 15 mL in total will be taken to perform standard laboratory assessments. If necessary, some more blood may be taken for a control examination in case of any problems. You will be requested to provide a urine sample to perform standard laboratory assessments.

You should be non-smoker or ex-smoker for at least 6 months before drug administration to participate in this study and you should not smoke or use tobacco in any form (e.g., smoking or chewing) until the end of confinement (including washout period). You should not take OTC medications from 7 days and Rx medications from 30 days before drug administration until the end of confinement (including washout period). Alcohol consumption will not be allowed from 48 hours prior to the first drug administration until the end of the study. You will have to abstain from St John's Wort, vitamins, herbal remedies, food or beverages containing orange, grapefruit and/or pomelo from two weeks prior to the first study drug administration until the end of confinement (including washout period). Participants are also requested to avoid food or beverages containing xanthine (coffee, tea, cola, energy drinks, chocolate, etc.) and poppy seeds from 48 hours prior to the first drug administration until the end of confinement. Chewing gum is not allowed on drug administration days. Any intense physical exercise (such as running, weightlifting, dancing, etc.) will not be allowed during your stay in the unit. You should agree to use medically acceptable methods of contraception during the study and for a period of 30 days after the end of the study. Medically acceptable methods of contraception include using a condom with a female partner of childbearing potential who is using oral contraceptives, hormonal patch, implant or injection, intrauterine device, or diaphragm with spermicide. Complete abstinence alone can be used as a method of contraception.

All corridors and rooms will be continuously monitored by cameras throughout your hospitalisation in order to follow your compliance with the study. All records will be deleted at the end of the study in the course of 4 months.

Blood samples (4 mL each) for drug analysis will be taken at the following times: pre-dose and 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 1 hour, 1 hour 15 min, 1 hour 30 min, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 36 hours, 48 hours and 72 hours post dose in both study periods. A short intravenous catheter may be used for collecting blood samples until 12 hours post dose. If there is a problem with the catheter, it may be taken out or replaced with a new one. In case of taking out the catheter, blood will be taken with an injector. A total blood loss of approximately 195 mL is expected. In order to compare please know that 400 - 450 mL blood is taken from you during a blood donation.

**At the end of the study, your plasma will be separated from your blood samples for drug analysis and the separated plasma will be sent to an analytical center in Spain in order to finalise the study. The name and contact information of the contact person are as follows:**

[redacted]



Paraph of the Volunteer:

**Your biological material (plasma samples) will not be used for any purposes other than this study.**

**Plasma samples will be destroyed after completion of the analysis, completion of the study or when the storage period needed for the monitors, auditors and related health authorities to verify the information of the clinical trial has expired.**

**If you withdraw your consent, any samples that have been collected from you before the point of withdrawal will be analysed and the data obtained from these will be processed according to the Clinical Study Protocol. Any data collected from you after your withdrawal from the study will not be used for drug analysis purposes but only for safety purposes, if necessary. In case you withdraw from the study, your samples will be either returned to the clinic or destroyed once the analysis is completed.**

For admission and in order to make sure that we start the study with the right number of volunteers, we will book more volunteers than will be dosed. The decision as to who is to receive the study drug on the day of administration will be taken by the physician. Should you not be dosed, then you will be compensated with an amount of money that is proportional to the time you have spent in the study.

## Side Effects

The frequency classification is made as follows:

**Very common;** may affect more than 1 in 10 people; **Common;** may affect 1 to 10 people in 100; **Uncommon;** may affect 1 to 10 people in 1,000; **Rare;** may affect 1 to 10 people in 10,000.

The below given side effects were seen during treatment with etoricoxib:

**Very common:** stomach pain

**Common:** dry socket (inflammation and pain after a tooth extraction); swelling of the legs and/or feet due to fluid retention (oedema); dizziness, headache; palpitations (fast or irregular heartbeat), irregular heart rhythm (arrhythmia); increased blood pressure; wheezing or shortness of breath (bronchospasms); constipation, wind (excessive gas), gastritis (inflammation of the lining of the stomach), heartburn, diarrhoea, indigestion (dyspepsia)/stomach discomfort, nausea, being sick (vomiting), inflammation of the oesophagus, mouth ulcers; changes in blood tests related to your liver; bruising; weakness and fatigue, flu-like illness.

**Uncommon:** gastroenteritis (inflammation of the gastrointestinal tract that involves both the stomach and small intestine/stomach flu), upper respiratory infection, urinary tract infection; changes in laboratory values (decreased number of red blood cells, decreased number of white blood cells, platelets decreased); hypersensitivity (an allergic reaction including hives which may be serious enough to require immediate medical attention); appetite increases or decreases, weight gain; anxiety, depression, decreases in mental sharpness; seeing, feeling or hearing things that are not there (hallucinations); taste alteration, inability to sleep, numbness or tingling, sleepiness; blurred vision, eye irritation and redness; ringing in the ears, vertigo (sensation of spinning while remaining still); abnormal heart rhythm (atrial fibrillation), fast heart rate, heart failure, non-specific ECG changes, feeling of tightness, pressure or heaviness in the chest (angina pectoris), heart attack; flushing, stroke, mini-stroke (transient ischaemic attack), severe increase in blood pressure, inflammation of the blood vessels; cough, breathlessness, nose bleed; stomach or bowel bloating, changes in your bowel habits, dry mouth, stomach ulcer, duodenal ulcer, inflammation of the stomach lining that can become serious and may lead to bleeding and perforation, irritable bowel syndrome, inflammation of the pancreas; swelling of the face, skin rash or itchy skin, redness of the skin; muscle cramp/spasm, muscle pain/stiffness; changes in blood or urine tests relating to your kidney, serious kidney problems; chest pain; high levels of potassium in your blood, high levels of uric acid in your blood.

**Rare:** angioedema (an allergic reaction with swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing, which may be serious enough to require immediate medical attention)/anaphylactic/anaphylactoid reactions including shock (a serious allergic reaction that requires immediate medical attention); confusion, restlessness; liver problems (hepatitis); low blood levels of sodium; liver failure, yellowing of the skin and/or eyes (jaundice); severe skin reactions.



Paraph of the Volunteer:

## Risks

The side effects listed above are seen with etoricoxib. These are generally rare and in almost all cases (except for allergic drug reactions) and occur as a consequence of prolonged or high-dose therapy, but the possibility to experience them after a single dose remains. Any drug can cause unpredictable side effects and life threating events (including death) which are not included above.

During catheterization before blood sampling dizziness/syncope may be seen rarely in sensitive persons.

Any information that becomes available during the course of the study that may affect your willingness to take part in the study will be disclosed to you as soon as practicable.

For the study results it is very important that you follow the instructions and study rules given in this informed consent form and that have been mentioned by the investigator. You must be able to attend all the scheduled study visits. **If you don't come to all blood sampling time points mentioned above, this will be considered as a study violation.** You could be withdrawn from the study by the investigator if you violate the study rules or if you show evidence of an uncooperative attitude that disturbs the investigators or other participants of the study.

**This information is given to you by an investigator physician from the study team. Please ask the investigator physician presenting this information to you for an explanation of unclear terms.** Apart from the information given in the present information sheet, you have the right to ask for additional information at any time during the trial.

All volunteers have been insured. The insurer is only liable for damages provided that:

- You will only receive other medical treatment with the consent of the investigators except for emergencies.
- You or your relatives have to inform the insurer and the physician without delay of any damage to health that may have resulted from the clinical study (see telephone number on title page).

Provided that such compensation may be reduced or cancelled to the extent that you, by reason of contributory fault, are partly responsible for the injury (or where you have received equivalent payment for such injury under any policy of insurance effected for my benefit).

Some insurers treat participating in medical studies as a material fact which should be mentioned when making any proposal to a health related insurance and you should disclose your participation in this study if you are in the process of seeking or renewing any insurance. You should also check that your participation does not affect any of your existing policies.

## Benefits

You won't have any direct benefits from a total of two times that a single dose of the study drugs (120 mg of etoricoxib) will be administered to you in this study but it is planned that the community profits from a social and economic point of view.

## Reimbursements

As, you won't have any direct benefits from the study medication, you will be given a certain amount of money to compensate for your working days lost and the expenses that you had on transportation and communication due to your participation in the study; other than that no extra money will be paid to you for the use of plasma samples obtained in this study. If you violate the study rules (such as missing the blood sampling points, administration of not allowed foods or drugs, smoking) the amount of the money you will be given may be decreased or you may be withdrawn from the study before the study completion.

There will be no financial cost for you to participate in this study.

## Confidentiality

Study records will identify individual volunteers only by their initials and/or date of birth. Your identity will remain confidential. Study records will be used for scientific purposes only and will be passed on to the sponsor of this study. To guarantee a regular study progress, study monitors, auditors, the ethics committees and regulatory authorities are granted direct access to your medical records.



Paraph of the Volunteer:

The relevant persons are specially trained for this purpose and are obliged to maintain professional discretion. They may only pass on personal data in an anonymous form. The results of this trial will be subjected to a computer evaluation after the possibility for any personal identification of the participants in the trial has been excluded.

The confidential nature of your records will be respected at all times. The requirements in regards to subject's confidentiality and handling of personal identifiable data stated in the regulation for data protection will be fulfilled. These conditions are stated in Annex 1 of this document.

The plasma samples obtained from this study won't be used for commercial purposes excluding intellectual property and patent rights.

### Sharing the Results

We may publish the results of the study so that other interested people may learn from our research but your confidential and personal information will not be shared.

### Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and your rights will still be fully respected.

### Alternatives to Participating

As the objective of this study is not to treat any disorders, there are no alternative treatments or approaches.

### Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact the Principal Investigator, whose contact information is given on page 1 of this Informed Consent Form.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

.....
.....
.....

*(This section is for the investigator who gives you the information in case any discussion points about the research arise during the information meeting with volunteers)*



Paraph of the Volunteer:

# *ANNEX I: PERSONAL DATA PROTECTION*

**Dear volunteer,**

Since May 25th, 2018, the new EU legislation on personal data, specifically the Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27th, 2016 on Data Protection (RGPD), has been fully applicable. Therefore, it is relevant that you know the following information:

- The Clinical Unit and the Sponsor are both respectively responsible for the processing of your data and engaged to comply with the data protection regulations in force.
- The data collected for the study will be identified by a code, so that it does not include information that can identify you, and only your study doctor/collaborators will be able to relate these data to you and your medical history. Therefore, your identity will not be disclosed to anyone other than the health authorities, when required or in cases of medical urgency. The Research Ethics Committees, the representatives of the Health Authority in matters of inspection and the personnel authorized by the Sponsor, may only access to check personal data, clinical study procedures and compliance with the rules of good clinical practice (always maintaining the confidentiality of information).
- The Clinical Unit and the Sponsor will take appropriate measures to ensure the protection of your privacy and will not allow your data to be cross-referenced with other databases which would allow your identification.
- According to the data protection legislation, you may exercise your rights of access, modification, opposition and cancellation of data, limit the processing of data that is incorrect, request a copy or transfer to a third party (portability) of the data you have provided for the study. To exercise your rights, please contact the principal Investigator of the study at Erciyes University Hakan Cetinsaya GCP and Research Center, [redacted]
- We remind you that data cannot be deleted even if you cease to participate in the trial in order to guarantee the validity of the research and to comply with legal duties and drug authorization requirements. You also have the right to contact with the competent Data Protection Authority if you are not satisfied.
- The Clinical Unit and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Thereafter, your personal information will only be retained by the health care facility and by the sponsor for other scientific research purposes if you have given your consent to do so and if permitted by applicable law and ethical requirements.
- If we transfer your encrypted data to our group entities, service providers or cooperating scientific researchers located in third countries or an international organization, your data will be protected by suitable safeguards such as contracts or other mechanisms issued by the corresponding Data Protection Authorities. If you require further detail, you can contact the Sponsor's representative: [redacted]



Paraph of the Volunteer:

# *CERTIFICATE OF CONSENT*

On |__|__| |__|__|__| |__|__| , the Investigator
DD MMM YY

_____ informed me about the structure, meaning, risks and aim of the clinical trial. I have been given a full explanation of the nature, purpose, likely duration of the study and what I will be expected to do and I have been advised about any discomfort and possible ill-effects on my health or well-being.

I have given all information about my previous and present illnesses, together with any medication or drugs I have taken within the last 6 months, and about any consultation that I have had with any physician in the last 6 months and any medications I am planning to take.

I agree to comply with any instruction given during the study and to co-operate with the investigators and to tell the investigators immediately if I suffer any deterioration in my health or well-being or any unexpected or unusual symptoms whenever they have arisen. I have further informed the investigators of any other volunteer studies in which I have previously taken part.

**I have read the foregoing information. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.**

**I have read the whole informed consent form. Written and verbal information about the study for which the objective and purpose are stated above is given by the doctor, whose name is written below. I am participating voluntarily in the study and I know that I am free to withdraw from the clinical study at any time without giving reasons. I accept to participate in the study without any pressure and enforcements.**

**Print Name and Surname of Participant:** _____

**Signature of Participant:** _____

**Date:** |__|__| |__|__|__| |__|__|
DD MMM YY



Paraph of the Volunteer:

**Statement by the Investigator**

**I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant fully understood the following points:**

**1. Ethical Considerations**

**2. Risks and benefits of the study**

**3. Details about the study procedures**

**I confirm that the participant was given an opportunity to ask questions about the study, and that all questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.**

**A copy of this ICF has been provided to the participant.**

**Print Name and Surname of Investigator:** _____

**Signature of Investigator:** _____

**Date:** |__|__| |__|__|__| |__|__| DD MMM YY **Time:** |__|__| : |__|__| hour min

* Referring to the Turkish Good Clinical Practice Guideline (13 November 2015), article 10.14 studies which are not treatment based should be performed in volunteers who can sign and date the informed consent forms. That's why a place for the signatures of the legal representatives and witness' has not been created.



Paraph of the Volunteer:

# Appendix

## 21.3. Form For Serious Adverse Events Reports

Screening No: |__|__|__|__|
and/or
Volunteer No: |__|__|__|__|

# FORM FOR SERIOUS ADVERSE EVENT REPORTS

## Study Title

**Randomized, open-label, single-dose, two-sequence, two-period, crossover, comparative, oral bioequivalence study of Exib 120 mg etoricoxib film-coated tablets (PrJSC "Pharmaceutical firm "Darnitsa") and Arcoxia 120 mg etoricoxib film-coated tablets (Merck Sharp&Dohme B.V.) in healthy, adult volunteers under fasting conditions**

**CLINICAL FACILITY**
Erciyes University Hakan Çetinsaya
İyi Klinik Uygulama ve Araştırma Merkezi,
IKUM (Center for GCP), Erciyes University,
[redacted]

**Clinical Study Code: 20ANE-3489C**

**Sponsor Study Code: ETR01-E**

Without regard to the suspicious causality with the study drug, all adverse events which have the following characteristics will be reported via filling this form.

All serious adverse events which;

- Results in death, is life threatening,
- Requires inpatient hospitalization or prolongs inpatient hospitalization,
- Results in persistent or significant disabling/ incapacity, results a congenital anomaly/birth defect,
- Results in serious medical event (which threats volunteer's life and may requires medical/surgical operation to prevent the results mentioned above).

| | |
|---|---|
| **INITIAL REPORT ☐** | **FOLLOW-UP REPORT ☐** |
| **INITIALS OF THE NAME AND SURNAME OF THE VOLUNTEER:** | |
| **VOLUNTEER NO:** | \|__\|__\|__\|__\| |
| **GENDER:** | **FEMALE ☐** **MALE ☐** |
| **DATE OF BIRTH:** | _____ / _____ /_____ (dd) (mmm) (yyyy) |
| **HEIGHT:** | |
| **WEIGHT:** | |
| **MEDICAL HISTORY OF THE VOLUNTEER:** | |

Screening No: |__|__|__|__|
and/or
Volunteer No: |__|__|__|__|

| **THE STUDY DRUG:**<br>**(in blinded studies, all the drugs which are likely to be taken by the volunteer should be specified)** | | |
|---|---|---|
| **MEDICATION** | **DOSAGE** | **INDICATION** |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

| **THE ONSET DATE OF THE VOLUNTEER TO THE ACTIVE STUDY DRUG:** | _____ / _____ /_____<br>(dd) (mmm) (yyyy) |
|---|---|

| **CONCOMITANT MEDICATIONS (PHARMACEUTICALS OR NONPHARMACEUTICALS)** | | | | |
|---|---|---|---|---|
| **MEDICATION** | **DOSAGE** | **INDICATION** | **DATE OF ONSET** | **DATE OF CESSATION** |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

| **DECRIPTION OF THE SERIOUS ADVERSE EVENT:** | |
|---|---|
| **ONSET DATE OF THE SERIOUS ADVERSE EVENT:** | _____ / _____ /_____<br>**(dd) (mmm) (yyyy)** |

Screening No: |__|__|__|__|
and/or
Volunteer No: |__|__|__|__|

| THE PROCESS FOLLOWED FOR THE SERIOUS ADVERSE EVENT: | |
|---|---|
| **DOSAGE OF THE STUDY DRUG** (tick only one) | ☐ Not changed<br>☐ Increased<br>☐ Decreased<br>☐ Temporarily stopped<br>☐ Treatment finalized |
| **VOLUNTEER IS WITHDRAWN** | ☐ |
| **VOLUNTEER IS TREATED** specify | ☐ _____ |
| **OTHER** specify | ☐ _____ |
| **NO TREATMENT** | ☐ |

| CESSATION OF THE SERIOUS ADVERSE EVENT | |
|---|---|
| **STILL PRESENT?** | ☐ Yes ☐ Not determined<br>☐ No – Resolved Date: ___ /____ /_____<br>(dd) (mmm) (yyyy) |
| **IS THE STUDY DRUG THE MOST SUSPECTED CAUSE OF THE SERIOUS ADVERSE EVENT?** | ☐ Yes ☐ No<br>☐ Not determined |
| **IF THE ANSWER IS NO; WHAT IS THE MOST SUSPECTED CAUSE OF THE ADVERSE EVENT?** (tick only one) | ☐ Investigational disease<br>☐ Concomitant disease<br>Specify:<br>_____<br>☐ Concomitant medication or other treatments<br>Specify:<br>_____<br>☐ Other<br>Specify:<br>_____ |

Screening No: |__|__|__|__|
and/or
Volunteer No: |__|__|__|__|

| | | | |
|---|---|---|---|
| **IS AUTOPSY DONE:** | ☐ **Yes** | ☐ **No** | ☐ **Not determined** |
| **IF YES, SPECIFY THE DETAILED FINDINGS:** | | | |
| **COMMENTS AND ADDITIONALS*:** | | | |

* Other additional information may be added to this section. Furthermore if this a follow-up report; the information which is different from the first report may be reported in this section.

| **INVESTIGATOR** | |
|---|---|
| **NAME AND SURNAME:** | |
| **PHONE:** | |
| **E-MAIL:** | |
| **ADDRESS:** | |

**SIGNATURE** **DATE**

_____ / _____ / _____
**(dd) (mmm) (yyyy)**

# Appendix

## 21.4. Acceptable Time Windows for Post-dose Clinical Procedures

# Acceptable Time Windows for Post-dose Clinical Procedures

Scheduled post-dose clinical procedures should be performed within the below time windows. Procedures performed outside of these windows will be considered protocol deviations and will be reported in the CSR.

| Procedure | Time window |
|---|---|
| 200 mL of water (Day 1) | + 5 min |
| Lunch (Day 1) | + 10 min |
| Dinner (Day 1) | - 10 min / + 10 min |
| AE checks | - 30 min / + 30 min |
| Vital signs | - 10 min / + 30 min |