Clinical Trial Protocol

	Document Number: c22345272-01
EudraCT No.:	Not applicable
BI Trial No.:	0107-0277
BI Investigational Product:	UHAC 62 XX, Meloxicam, Movalis®
Title:	An open-label, randomised, single-dose, two-way crossover study in healthy male and female volunteers to evaluate the relative bioavailability of a new oral formulation of meloxicam, Movalis® capsules 15 mg, versus Movalis® tablets 15 mg, after administration under fasting state.
Clinical Phase:	Bioequivalence study
Lay Title	A study to compare the amount of meloxicam in the blood when it is taken as capsules or as tablets.
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Address: . Phone number: Fax:
Status:	Final Protocol
Version and Date:	Version: 1.0 Date: 28 May 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Movalis® capsules 15 mg			
Name of active ingredient: UHAC 62 XX, meloxicam, Movalis®			
Protocol date: 28 May 2018	**Trial number:** 0107-0277		**Revision date:** Not applicable

Title of trial:	An open-label, randomised, single-dose, two-way crossover study in healthy male and female volunteers to evaluate the relative bioavailability of a new oral formulation of meloxicam, Movalis® capsules 15 mg, versus Movalis® tablets 15 mg, after administration under fasting state.
Principal Investigator:	Adress: Phone number: Fax:
Trial site(s):	Address:
Clinical phase:	Bioequivalence study
Objectives:	Primary objective: To investigate the relative bioavailability of Movalis® capsules 15 mg versus Movalis® tablets 15 mg. Secondary objectives: 1. To establish bioequivalence of Movalis® capsules 15 mg versus Movalis® tablets 15 mg. 2. The assessment of safety and tolerability will be an additional objective of this trial.
Methodology:	This will be an open-label, randomised, single-dose, two-way crossover study in healthy male and female volunteers conducted in one clinical trial site in Russian Federation.
No. of subjects:	
total entered:	26
each treatment:	Movalis® capsules 15 mg (Test formulation , T) – 26, Movalis® tablets 15 mg (Reference formulation, R) – 26
Diagnosis:	Not applicable
Main criteria for inclusion:	Male and female subjects aged 18-45, inclusive. Body mass index by Quetelet between 18.50 -29.99 kg/m2, inclusive.
Test product:	Movalis® capsules (T)
dose:	15 mg
mode of admin.:	Oral with 200 mL of water after an overnight fast of at least 10 h

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Movalis® capsules 15 mg			
Name of active ingredient: UHAC 62 XX, meloxicam, Movalis®			
Protocol date: 28 May 2018	**Trial number:** 0107-0277		**Revision date:** Not applicable

Comparator product:	Movalis tablets (R)
dose:	15 mg
mode of admin.:	Oral with 200 mL of water after an overnight fast of at least 10 h
Duration of treatment:	One day (single dose) for each treatment
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-t} and $C_{max.}$ Secondary endpoints: $AUC_{0-\infty}$.
Criteria for safety:	Vital signs (blood pressure, pulse rate, temperature, respiratory rate), global assessment, physical examination, 12-lead ECG, laboratory tests, adverse events.
Statistical methods:	Two-sided 90% CIs for the intra-subject ratio (as estimated by the ratio of geometric means) of each of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} will be calculated to determine whether the CIs are contained in the acceptance range for bioequivalence (80-125% for AUC_{0-t}; 80-125% for C_{max}). The drugs will be considered bioequivalent if: • the limits of the estimated confidence interval for AUC_{0-t} are within 80.00–125.00%; • the limits of the estimated confidence interval for C_{max} are within 80.00–125.00%: The statistical model will be ANOVA on log-transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs will be based on the residual error from ANOVA. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. Descriptive statistics for all other parameters will be calculated.

FLOW CHART

Phase	Visit	Day (time window)	Planned Time after drug administration [h:min][1]	Time window for PK blood sampling [h:min]	Hospitalization	Randomisation	Drug administration	Routine laboratory tests[2]	Exclusionary testing	Blood sampling for PK	Physical examination	12-lead ECG	Vital signs[3]	Global assessment	Adverse events	Meals	Concomitant medication
Screening[4]	1	-14 to -1						x	x[5]		x	x	x		x		x
Period I	2	-1	-16:00 – -10:00		x	x			x[6]		x	x[7]	x	x	x		x
		1	-2:00	-2:00 – 0:01						x			x		x		x
			0:00				x										
			0:30	±0:02						x							
			1:00	±0:02						x							
			2:00	±0:02						x							
			3:00	±0:05						x							
			4:00	±0:05						x						x	
			5:00	±0:05						x							
			6:00	±0:05						x			x		x	x	x
			7:00	±0:10						x							
			8:00	±0:10						x							
			9:00													x	
			10:00	±0:10						x							
			11:00													x	
			12:00	±0:10						x			x		x		x
		2	24:00	±0:15						x	x		x	x	x		x
			32:00	±0:15						x							

[1] The time points are strict for the T/R drug administration and PK blood sampling.

[2] Routine laboratory tests include haematology, clinical chemistry and urinalysis.

Hematology: erythrocyte sedimentation rate (ESR), hematocrit (Hct), haemoglobin (Hb), erythrocytes/ red blood cells (RBC), platelet count, leucocytes/white blood cells (WBC), differential WBC (neutrophils, eosinophils, basophils, monocytes, lymphocytes). Test is performed at fasted state.

Clinical chemistry: total protein, glucose, total cholesterol, total bilirubin, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP) electrolytes (Na, K, Ca). Test is performed at fasted state.

Urinalysis: pH, protein, glucose, ketone, bilirubin, urobilinogen, RBC, nitrite, WBC. Urine-Sediment: bacteria; epith cells; RBC/erythrocytes; WBC/leucocytes.

If clinical chemistry analysis revealed ALT and/or AST values ≥3 fold ULN in conjunction with an elevation of total bilirubin of ≥2 fold ULN, following laboratory tests should be repeated: ALT, AST, and bilirubin (total and direct) - within 48 to 72 h. If it is confirmed that ALT and/or AST values ≥3 fold ULN occur in conjunction with an elevation of total bilirubin of ≥2 fold ULN, hematology, serology and clinical chemistry analysis must be performed and made available to the investigator and to BI as soon as possible

[3] Vital signs: systolic and diastolic blood pressure (BP), pulse rate (PR), body temperature, respiratory rate.

[4] In addition to procedures specified in the Flow Chart at screening the following procedures are also performed: providing volunteer with subject information, receiving signed informed consent, collection data about demographics, smoking and alcoholic history, relevant medical history, concomitant medication, measuring body weight, height and calculation of body-mass-index (BMI).

[5] At screening exclusionary testing includes: infectious serology (qualitative HbsAg test, qualitative test for anti-HCV total, qualitative test for anti-HIV1/2, test for syphilis); urine test for β-HCG (test strips for women); urine drug screening (test strips for cannabis, benzodiazepine, barbiturates, opiates, cocaine, amphetamines); breath test for alcohol.

[6] On Day -1 of period I to confirm subject's eligibility the following exclusionary testing is achieved: urine test for β-HCG (test strips for women); urine drug screening (test strips for cannabis, benzodiazepine, barbiturates, opiates, cocaine, amphetamines); breath test for alcohol.

[7] If 12-lead ECG is taken on Day -7-1 at screening, the results can be used on Day 1 in Period I.

Phase	Visit	Day (time window)	Planned Time after drug administration [h:min][1]	Time window for PK blood sampling [h:min]	Hospitalization	Randomisation	Drug administration	Routine laboratory tests[2]	Exclusionary testing	Blood sampling for PK	Physical examination	12-lead ECG	Vital signs[3]	Global assessment	Adverse events	Meals	Concomitant medication
		3	48:00	±0:15						x	x		x	x	x		x
		4	72:00	±0:15				x		x	x		x	x	x		x
Wash-out[8]		7 days															
Period II	3	7	-16:00 – -10:00		x				x[9]		x	x	x	x	x		
		8	-2:00	-2:00 – 0:00						x	x		x		x		x
			0:00				x										
			0:30	±0:02						x							
			1:00	±0:02						x							
			2:00	±0:02						x							
			3:00	±0:05						x							
			4:00	±0:05						x						x	
			5:00	±0:05						x							
			6:00	±0:05						x			x	x	x	x	x
			7:00	±0:10						x							
			8:00	±0:10						x							
			9:00													x	
			10:00	±0:10						x							
			11:00													x	
			12:00	±0:10						x			x	x	x		x
		9	24:00	±0:15						x	x		x	x	x		x
			32:00	±0:15						x							
		10	48:00	±0:15						x	x		x	x	x		x
		11	72:00	±0:15				x		x	x	x	x	x	x		x
Follow-up	4	18							x[10]		x		x		x		x

[8] The duration of the wash-out period is calculated from the time of administration of the study drug in the first study period to the time of administration of the study drug in the second study period. The interval between the discharge of the study subject from the hospital in the first period and the hospitalization of the study subject in the second study period is about 3.5 days

[9] On Day 7 in period II to confirm subject's eligibility the following exclusionary testing is achieved: urine test for β-HCG (test strips for women); urine drug screening (test strips for cannabis, benzodiazepine, barbiturates, opiates, cocaine, amphetamines); breath test for alcohol.

[10] Only urine test for β-HCG (test strips for women).

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ABBREVIATIONS

AE	Adverse event
ACR20	20% improvement according to American College of Rheumatology (ACR) response criteria
AESI	Adverse events of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-t}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body Mass Index (weight divided by height squared)
BLQ	Below limit of quantification
ß-HCG	Beta-human chorionic gonadotrophin
BP	Blood pressure
CA	Competent authority
CK	Creatinine kinase
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
$C(')_t$	Measured (predicted) concentration of the analyte in plasma at the last time t at which quantification of the analyte in plasma was still possible
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRO	Contact research organisation
CRF	Case report form
CTMF	Clinical trial master file
CTP	Clinical trial protocol
CTR	Clinical trial report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Arithmetic coefficient of variation
CYP	Cytochrome
DILI	Drug induced liver impairment
δ	Bioequivalence margin
ECG	Electrocardiogram

EDTA	Ethylendiaminetetraacetic acid
EDC	Electronic data capture
EOT	End of trial
F	Absolute bioavailability factor
FAS	Full Analysis Set
eCRF	Electronic case report form
GCP	Good clinical practice
GI	Gastro-intestinal
gMean	Geometric mean
h	hours
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HPC	Human Pharmacology Centre
HR	Heart rate
IB	Investigator's Brochure
ICH	International committee on harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
ISF	Investigator site file
kg	Kilograms
HPLC-MS/MS	High performance liquid chromatography, tandem mass spectrometry
Ln	Natural logarithm
LOQ	Limit of quantification
MedDRA	Medical dictionary for drug regulatory affairs
mg	Milligrams
ml	Milliliters
NOA	Not analysed
NOAEL	No observed adverse effect level
NOTEL	No toxic effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NSAID	Non-steroid anti-inflammatory drug
PK	Pharmacokinetics
PD	Pharmacodynamic(s)
PR	Pulse rate
p.o.	Oral
PR	Pulse rate
R	Reference treatment
RA	Rheumatoid arthritis
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SCR	Screening

SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test treatment
q.d.	Quaque die, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The active ingredient of Movalis® formulations is meloxicam. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties, ATC: M01AC06.

In clinical trials meloxicam was shown to be safe and effective in the treatment of symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Meloxicam was first registered as tablets (7.5 mg, 15 mg), capsules (7.5 mg, 15 mg) and suppositories (15 mg) with the trademark Mobic® in France on 8 May 1995. This date was defined as the international birthdate of meloxicam. Since then, registrations have been obtained worldwide for the dosage forms and strengths mentioned above and further formulations (oral suspension 7.5 mg/5ml, solution for injection 15 mg/1.5ml, capsule 7.5 mg, table 10 mg, suppository 7.5 mg). These registrations were granted not only as Mobic®, but also with further trademarks, e.g. Movalis®, Hexaphlogin®, Mobicox®, and Movatec®. Meloxicam is currently authorised and marketed in more than 100 European and non-European countries.

1.2 DRUG PROFILE

The drug profile of meloxicam is presented briefly in this section. For details refer to Meloxicam Investigator's Brochure, section "Guidance for the investigator" [c22930410].

1.2.1 Composition of Movalis® oral formulations

Composition of Test formulation: Movalis® capsules 15 mg, Boehringer Ingelheim Ellas A.E, Greece.

INN	Meloxicam
Brand name	Movalis®
Chemical name	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
Formulation	Capsule
Active substance	meloxicam15 mg
Excipients	Capsule content: sodium citrate, lactose monohydrate, maize starch, magnesium stearate. Capsule shell: gelatin, indigo carmine, yellow iron oxide, titanium dioxide
Pharmaco-therapeutic group	Non-steroidal anti-inflammatory drug
ATC	M01AC06

Composition of Reference formulation: Movalis® tablets 15 mg, Boehringer Ingelheim Ellas A.E., Greece and Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

INN	Meloxicam
Brand name	Movalis®
Chemical name	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
Formulation	Tablet
Active substance	meloxicam15 mg
Excipients	sodium citrate, lactose monohydrate, microcrystalline cellulose, povidone K25, colloidal anhydrous silica, crospovidone, magnesium stearate
Pharmaco-therapeutic group	Non-steroidal anti-inflammatory drug
ATC	M01AC06

The choice of the drug Movalis® (Boehringer Ingelheim Ellas A.E., Greece and Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.) tablets 15 mg as a comparator is due to the following reasons:

- Movalis® is an original medicinal product, the quality, safety and efficacy of which were established during registration in the territory of the Russian Federation, which corresponds to the requirements of the Guidelines "Evaluation of bioequivalence of medicines" (2008) and Decision of the Eurasian Economic Commission No. 85 of 03.11.2016 "On Approval of the Rules for Conducting studies of bioequivalence of drugs in the framework of the Eurasian Economic Union"[Decision of the Eurasian Economic Commission No. 85].
- Compared drugs are produced in comparable dosage forms-tablets and capsules [Decision of the Eurasian Economic Commission No. 85].
- Compared preparations contain the active substance in an equal amount, which is the largest dosage of the study drug and the reference preparation: 15 mg.
- The excipients included in the composition of the drugs are well known and should not influence the pharmacokinetics of the drugs being compared.

The choice of the reference drug batch will be made taking into account the results of quantitative determination of the active substance content and data on its dissolution [Decision of the Eurasian Economic Commission No. 85].

1.2.2 Pharmacodynamics

Meloxicam is a non-steroidal anti-inflammatory drug, a derivative of enolic acid, and has anti-inflammatory, analgesic and antipyretic effects. The pronounced anti-inflammatory effect of meloxicam is established on all standard models of inflammation. The mechanism of action of meloxicam is its ability to inhibit the synthesis of prostaglandins - known inflammatory mediators.

Meloxicam in vivo inhibits the synthesis of prostaglandins at the site of inflammation to a greater extent than in the mucous membrane of the stomach or kidneys. These differences are associated with a more selective inhibition of cyclooxygenase-2 (COX-2) compared to cyclooxygenase-1 (COX-1). In clinical trials, the frequency of perforations in the upper gastrointestinal tract, ulcers and bleeding that were associated with the use of meloxicam was low and depended on the magnitude of the dose of the drug.

1.2.3 Pharmacokinetics

Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration. After a single application of meloxicam maximum concentration of drug in plasma is achieved within 5-6 hours. Simultaneous intake of food and inorganic antacids does not alter absorption. When given orally (in doses of 7.5 and 15 mg), meloxicam concentrations are proportional to the doses. Steady state of pharmacokinetics is achieved within 3-5 days The range of differences between the maximum and basal concentrations of the drug after its administration once a day is relatively small and when using a dose of 7.5 mg 0.4-1.0 μg / ml, and when using a dose of 15 mg - 0.8-2.0 μg / ml (given respectively, the values of C_{min} and C_{max} during the steady state of pharmacokinetics), although values outside this range were also noted. The maximum concentration of meloxicam in plasma during the steady state of pharmacokinetics is reached 5-6 hours after ingestion.

Distribution

Meloxicam is strongly bound to plasma proteins, mainly with albumin (99%). It penetrates into the synovial fluid, the concentration in the synovial fluid is approximately 50% of the concentration in the plasma. The volume of distribution after multiple oral doses of meloxicam (in doses from 7.5 mg to 15 mg) is about 16 liters, with a coefficient of variation of 11 to 32%.

Biotransformation

Meloxicam is almost completely metabolized in the liver with the formation of 4 pharmacologically inactive derivatives. The main metabolite, 5'-carboxymeloxicam (60% of the dose value), is formed by oxidation of the intermediate metabolite, 5'-hydroxymethylmeloxicam, which is also excreted, but to a lesser degree (9% of the dose value). In vitro studies have shown that CYP2C9 plays an important role in this metabolic transformation, the CYP3A4 isoenzyme plays an additional role. In the formation of the other two metabolites (which constitute, respectively, 16% and 4% of the dose value), peroxidase takes part, the activity of which, probably, varies individually.

Elimination

Meloxicam is excreted through the intestines and kidneys, mainly in the form of metabolites. In unchanged form with feces less than 5% of the daily dose is excreted, in the urine in

unchanged form the drug is found only in trace amounts. The average half-life of meloxicam varies from 13 to 25 hours.

Plasma clearance is an average of 7 - 12 ml/min after a single dose of meloxicam.

Patients with hepatic/renal insufficiency

Lack of liver function, as well as mild renal failure, does not significantly affect the pharmacokinetics of meloxicam. The rate of excretion of meloxicam from the body is much higher in patients with moderate renal insufficiency. Meloxicam binds less strongly to plasma proteins in patients with terminal renal insufficiency. With terminal renal failure, an increase in volume distribution can lead to higher concentrations of free meloxicam, so in these patients the daily dose should not exceed 7.5 mg.

Elderly

Older patients have similar pharmacokinetic parameters in comparison with young patients. In elderly patients, the average plasma clearance during the equilibrium state of pharmacokinetics is slightly lower than in young patients. Older women have higher AUC values (area under the concentration-time curve) and a longer half-life, compared to young patients of both sexes.

1.2.4 Indications

The information is based on the current version of the instructions for the use of the reference drug in Russian Federation.

- Osteoarthritis (arthrosis, degenerative diseases of joint), including those with pain component;
- Rheumatoid arthritis;
- Ankylosing spondylitis;
- Other inflammatory and degenerative musculoskeletal system diseases, such as arthropathy, dorsopathy (e.g., sciatica, lower back pain, shoulder-related tendinitis and other) accompanied by pain.

1.2.5 Contraindications

The information is based on the current version of the instructions for the use of the reference drug in Russian Federation.

- Hypersensitivity to the active ingredient or excipients of the product;
- Complete or incomplete combination of bronchial asthma, recurrent polyposis of the nose and paranasal sinuses, angioedema or urticaria caused by intolerance to acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs due to the existing probability of cross sensitivity (including history of these conditions);

- Erosive-ulcerative lesions of the stomach and duodenum at the stage of exacerbation or recent lesions;
- Inflammatory diseases of the intestine – Crohn's disease or ulcerative colitis at the stage of exacerbation;
- Severe hepatic insufficiency;
- Severe renal insufficiency (if hemodialysis is not conducted, creatinine clearance is less than
- 30 mL/min, and also in confirmed hyperkalemia), a progressive kidney disease;
- Active gastrointestinal bleeding, recent cerebrovascular diseases or the established diagnosis of systemic hemorrhagic diseases;
- Pronounced uncontrolled heart failure;
- Pregnancy;
- Breast feeding;
- Therapy of perioperative pains during coronary artery bypass grafting (CABG);
- Children aged less than 12 years;
- Rare hereditary intolerance of galactose (the maximum daily dose of the product with the meloxicam dosage of 7.5 mg and 15 mg contains 47 mg and 20 mg of lactose, respectively).

1.2.6 Special warning and precautions

The information is based on the current version of the instructions for the use of the reference drug in Russian Federation. Due to increased risk of adverse reactions caution should be exercised when treating patients with following conditions:

- a history of gastrointestinal diseases (peptic ulcer of the stomach and duodenum, diseases of the liver);
- congestive heart failure;
- renal insufficiency (creatinine clearance 30-60 mL/min);
- coronary artery disease;
- cerebrovascular diseases;
- dyslipidemia/hyperlipidemia;
- diabetes mellitus;
- concomitant therapy with the following agents: oral glucocorticosteroids, anticoagulants (including warfarin), antiaggregants, selective inhibitors of serotonin reuptake (including citalopram, fluoxetine, paroxetine, sertraline);
- diseases of the peripheral arteries;
- elderly age;
- a prolonged use of NSAIDs;
- smoking;
- frequent consumption of alcohol.

1.2.7 Dosage and administration

The information is based on the current version of the instructions for the use of the reference drug in Russian Federation.

Osteoarthritis with pain syndrome: 7.5 mg a day. When necessary, the dose may be increased to 15 mg a day.

Rheumatoid arthritis: 15 mg a day. Depending on the therapeutic effect, the dose may be reduced to 7.5 mg a day.

Ankylosing spondylitis: 15 mg a day. Depending on the therapeutic effect, the dose may be reduced to 7.5 mg a day.

In patients with the increased risk of side reactions (history of diseases of the gastrointestinal tract, risk factors of cardiovascular diseases) it is recommended to begin treatment with the dose of 7.5 mg a day. (see Special warnings and precautions).

In patients with pronounced renal insufficiency receiving hemodialysis the dose should not exceed 7.5 mg a day.

General recommendations

As the potential risk of side reactions depends on the dose and duration of treatment, the maximum possible low doses and duration of treatment should be used.

The maximum recommended daily dose is 15 mg.

Combined use

The product should not be used concomitantly with other NSAIDs.

The total daily dose of MOVALIS used as different pharmaceutical forms should not exceed 15 mg.

Adolescents

The maximum dose in adolescents (12-18 years) is 0.25 mg/kg and should not exceed 15 mg.

Use of tablets

The product is contraindicated for children less than 12 years due to impossibility of adjustment of appropriate dosage for this age group.

The total daily dose should be taken as a single dose with food and water or other liquid.

1.2.8 Interactions

The information is based on the current version of the instructions for the use of the reference drug in Russian Federation.

- Other inhibitors of prostaglandin synthesis including glucocorticoids and salicylates – the concomitant administration with meloxicam increases the risk of formation of ulcers in the gastrointestinal tract and gastrointestinal bleedings (due to synergism of action). The concomitant administration with other NSAIDs is not recommended.
- Anticoagulants for oral administration, heparin for systemic use, thrombolytic agents – the concomitant administration with meloxicam increases the risk of bleeding. Thorough control of the coagulation system is necessary in case of the concomitant administration.
- Antithrombocytic agents, inhibitors of serotonin reuptake – the concomitant administration with meloxicam increases the risk of bleeding due to inhibition of thrombocyte function. Thorough control of the coagulation system is necessary in case of the concomitant administration.
- Preparations of lithium – NSAIDs increase the plasma level of lithium by decreasing its renal excretion. The concomitant use of meloxicam with lithium preparations is not recommended. If the concomitant administration is necessary, it is recommended to perform thorough control of the plasma concentration of lithium throughout the course of use of lithium preparations.
- Methotrexate – NSAIDs decrease renal secretion of methotrexate, thereby increasing its concentration plasma. The concomitant use of meloxicam and methotrexate (in the dosage of more than 15 mg a week) is not recommended. During the concomitant use thorough control of renal function and blood count is recommended. Meloxicam may enhance hematological toxicity of methotrexate, particularly in patients with renal impairment. The concomitant use of meloxicam and methotrexate for 3 days increases the risk of increasing toxicity of the latter.
- Contraception – the data are available that NSAIDs may decrease effectiveness of contraceptive devices, however, this has not been proved.
- Diuretics – the use of NSAIDs at dehydration of patients is associated with the risk of developing acute renal insufficiency.
- Antihypertensive agents (beta-adrenoblockers, inhibitors of angiotensin converting enzyme, vasodilating agents, diuretics). NSAIDs reduce the effect of antihypertensive agents by inhibition of prostaglandins which possess vasodilating properties.
- Angiotensin-II receptor antagonists, as well as inhibitors of angiotensin converting enzyme, at the concomitant use with NSAIDs enhance a decrease of glomerular filtration and that may result in development of acute renal insufficiency, particularly in patients with renal impairment.
- Cholestyramine, by binding meloxicam in the gastrointestinal tract, causes its more rapid elimination.
- NSAIDs may enhance nephrotoxicity of cyclosporin due to the effect on renal prostaglandins.
- Pemetrexed – at concomitant use of meloxicam and pemetrexed in patients with creatinine clearance from 45 to 79 mL/min the use of meloxicam should be stopped at 5 days before a patient begins to take pemetrexed and may be resumed 2 days after

discontinuation of pemetrexed. If concomitant use of meloxicam and pemetrexed is needed, such patients should be under strict control, particularly with respect to myelosuppression and occurrence of side effects of the gastrointestinal tract. The concomitant use of meloxicam and pemetrexed is not recommended in patients with creatinine clearance less than 45 mL/min.

At the concomitant use of meloxicam with the medications possessing the known capacity to inhibit CYP 2C9 and/or CYP 3A4 (or are metabolized with participation of these enzymes), such as sulfonylureas or probenecid, the possibility of pharmacokinetic interaction should be considered.

At concomitant use with oral antidiabetic agents (e.g. sulphonylureas, nateglinide), CYP 2C9-mediated interactions are possible which may result in an increase of the blood concentration of both these agents and meloxicam. Patients who take meloxicam concomitantly with sulphonylureas or nateglinide should carefully control sugar level in blood due to the possibility of hypoglycemia developing.

No significant pharmacokinetic interactions were revealed during concomitant administration of antacids, cimetidine, digoxin and furosemide.

1.2.9 Pregnancy and lactation

The use of MOVALIS is contraindicated during pregnancy.

NSAIDs are known to pass into mother's milk, therefore the use of MOVALIS is contraindicated during breast feeding.

As an inhibitor of cyclooxygenase/prostaglandin synthesis, MOVALIS may influence fertility, and therefore it is not recommended for women who are planning pregnancy. Meloxicam may cause delay of ovulation. In view of this it is recommended to withdraw MOVALIS in women who have problems with conception and are undergoing examination for such problems.

1.2.10 Effects on ability to drive and use machines

The information is based on the current version of the instructions for the use of the reference drug in Russian Federation.

Special clinical trials of the effect of the product on the ability to drive cars and operate machines have not been conducted. However, when driving a car and operating machines the possibility of developing dizziness, drowsiness, visual disorder or other disorders of the central nervous system should be taken into consideration. Patients should be cautious while driving a car and operating machines.

1.2.11 Non-clinical studies

An extensive toxicological program confirmed that meloxicam has an acceptable safety profile.

Oral LD_{50} values ranged from about 98 mg/kg in female rats up to >800 mg/kg in mini-pigs. Intravenous values ranged from about 52 mg/kg in rats to 100 - 200 mg/kg in mini-pigs. Main signs of toxicity included reduced motor activity, anaemia, and cyanosis. Most deaths occurred as a consequence of gastric ulcers and subsequent perforation leading to peritonitis.

Repeated dose toxicity studies in rats and mini-pigs showed characteristic changes reported with other NSAIDs e.g. gastro-intestinal ulceration and erosions, and in the long term studies, renal papillary necrosis. Gastro-intestinal side effects were observed at oral doses of 1mg/kg and higher in rats, and of 3 mg/kg and above in mini-pigs. After intravenous administration doses of 0.4 mg/kg in rats and 9 mg/kg in mini-pigs caused gastro-intestinal lesions. Renal papillary necrosis occurred only in rats at doses of 0.6 mg/kg or higher doses after lifetime exposure to meloxicam.

Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits. Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher.

The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on an mg/kg dose basis (75 kg person). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described.

Meloxicam was not mutagenic in the Ames test, the host-mediated assay, and a mammalian gene mutation assay (V79/HPRT), nor is it clastogenic in the chromosomal aberration assay in human lymphocytes and the mouse bone marrow micronucleus test.

Carcinogenicity studies in rats and mice did not show a carcinogenic potential up to dose levels of 0.8 mg/kg in rats and 8 mg/kg in mice. In these studies meloxicam was chondro-neutral, i.e. it did not damage the articular cartilage following long-term exposure.

Meloxicam did not induce immunogenic reactions in tests on mice and guinea pigs. In several tests it was shown that meloxicam was less phototoxic than older NSAIDs but similar in this respect to both piroxicam and tenoxicam.

In local tolerance studies meloxicam was well tolerated by all tested routes of administration; intravenous, intramuscular, rectal, dermal, and ocular administration.

For further details see ‘Investigator’s Brochure’[c22930410].

1.2.12 Clinical studies

Osteoarthritis

The primary evidence for efficacy of meloxicam for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in two randomised placebo-controlled

trials (EU trial 107.42, U.S. trial 107.181) [U92-0541; U98-3221] and four randomised active-controlled trials conducted in E.U. (E.U trials 107.43, 107.44, 107.45, 107.63) [U93-2036; U93-2016; U93-2037; U93-2015].

The data both from 3-week, double-blind, placebo-controlled study and 3-months, double-blind, placebo-controlled study showed that meloxicam in doses of 7.5 mg and 15 mg was consistently superior to placebo, and the lowest effective dose was 7.5 mg once daily.

Data available from the four double-blind, active-controlled trials ranging from 6 weeks' to 6 months' duration demonstrated that the efficacy of meloxicam, in doses of 7.5 mg/day, 15 mg/day and 30 mg/day, was comparable to traditional NSAIDs piroxicam 20 mg/day and diclofenac SR 100 mg/day. The dose 30 mg/day was discontinued during the trials. The data suggested a dose response when comparing all trials.

Rheumatoid Arthritis

The primary evidence for use of meloxicam for the treatment of the signs and symptoms of rheumatoid arthritis was evaluated in two randomised placebo-controlled trials (Trial 107.35 and 107.183) [U93-2066; U99-3147] and three randomised active-controlled trials (Trial 107.14, 107.36, 107.61) [U93-2021; U92-0311; U93-2054].

In a 3-week, double-blind E.U. trial 107.35 meloxicam (7.5 mg and 15 mg daily) was compared to placebo. In a 12-week, double-blind, controlled U.S. trial107.183 meloxicam (7.5 mg, 15 mg, and 22.5 mg daily) was compared to placebo and diclofenac 2x75 mg daily. The primary endpoint in the studies was the ACR20 response rate, a composite measure of clinical, laboratory, and functional measures of rheumatoid arthritis (RA)-response. Patients receiving meloxicam 7.5 mg and 15 mg daily showed significant improvement in the primary endpoint compared with placebo. The lowest effective dose of meloxicam was 7.5 mg. No incremental benefit was observed with the 22.5 mg dose compared to the 15 mg dose.Meloxicam 7.5 mg, 15 mg and 22.5 mg were comparable to the active control drugs. Since efficacy of 7.5 mg may be low for the initial treatment of acute flares of RA, 15 mg is considered a more appropriate starting dose. The data suggest evidence for a dose response.

Data from the active-controlled trials (Trial 107.14, 107.36, 107.61) ranging from 3 weeks' to 6 months' duration showed that meloxicam 15 mg/day was as effective as piroxicam 20mg/day or naproxen 750 mg/day.

Ankylosing spondylitis

The primary evidence for use of meloxicam for the treatment of ankylosing spondylitis was established in one randomised controlled trial (Trial 107.98) [U98-0090; U97-0033]. In this 6-week, double-blind, controlled study meloxicam (15 mg and 22.5 mg daily) was superior to placebo in treating the signs and symptoms of ankylosing spondylitis. The lowest dose investigated is meloxicam 15 mg once daily. Both doses, meloxicam 15 mg and 22.5 mg, were comparable with regard to efficacy with no further increase in efficacy for the dose above 15 mg. Meloxicam 15 mg and 22.5 mg once daily were both comparable to piroxicam 20 mg daily. Effective symptom relief was maintained during long-term therapy (extension phase of the trial till one year).

In all clinical trials, gastro-intestinal adverse events overall were reported less frequently with meloxicam 7.5 mg and 15 mg than with the NSAIDs with which it has been compared, due

predominantly to a lower reporting incidence of events such as dyspepsia, vomiting, nausea and abdominal pain. The incidence of upper gastro-intestinal perforation, ulcers, and bleeds reported in association with meloxicam is low and dose dependent.

For further details see 'Investigator's Brochure' [c22930410].

1.2.13 Side effects

Below there are described side effects the relation of which with the use of MOVALIS was regarded as possible.

The side effects registered in the period of post-marketing use, the relation of which with the product use was evaluated as possible are asterisked (*).

Inside the system organ classes by the frequency of occurrence of side effects the following categories are used: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ /1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not established.

Blood and lymphatic system

Uncommon – anemia;

Rare – changes of blood count including changes of the differential white cell count, leukopenia, thrombocytopenia.

Immune system

Uncommon – other immediate hypersensitivity reactions*;

Not established – anaphylactic shock*, anaphylactoid reaction*.

Nervous system

Common – headache;

Uncommon – dizziness, drowsiness.

Psychiatric disorders

Common – altered mood*;

Not established – mental confusion*, disorientation*.

Sense organs

Uncommon – vertigo;

Rare – conjunctivitis*, disorders of vision including blurred vision*, tinnitus.

Gastrointestinal tract

Common – abdominal pain, dyspepsia, diarrhea, nausea, vomiting;

Uncommon – latent or overt gastrointestinal bleeding, gastritis*, stomatitis, constipation, abdominal distension, belching;

Rare – gastroduodenal ulcers, colitis, esophagitis;

Very rare – perforation of the gastrointestinal tract.

Liver

Uncommon – transient changes of liver function parameters (e.g., increased activity of transaminases or bilirubin);

Very rare – hepatitis*.

Skin and subcutaneous tissues

Uncommon – angioedema*, itching, skin rash;

Rare – toxic epidermal necrolysis*, Stevens-Johnson syndrome*, urticaria;

Very rare – bullous dermatitis*, multiform erythema*;

Not established – photosensitization.

Respiratory system

Rare – bronchial asthma in patients with allergy to acetylsalicylic acid or other NSAIDs.

Cardiovascular system

Uncommon – increased blood pressure, feeling of facial flushing;

Rare – palpitation.

Urinary system

Uncommon – changes of kidney function parameters (increased level of creatinine and/or urea in serum), disorders of urination including acute urine retention*;

Very rare – acute renal insufficiency*.

Reproductive system and breast

Uncommon – ovulation delayed*;

Not established – infertility female*.

The concomitant use with medications suppressing the bone marrow (e.g., methotrexate) may induce cytopenia.

Gastrointestinal bleeding, ulcer or perforation may lead to fatal outcome.

As with other NSAIDs, the possibility of occurrence of interstitial nephritis, glomerulonephritis, renal medullary necrosis, nephrotic syndrome is not excluded.

1.2.14 Special instructions

Patients with diseases of the gastrointestinal tract should be under regular observation. MOVALIS should be discontinued at the occurrence of an ulcerative lesion of the gastrointestinal tract or gastrointestinal bleeding.

Ulcers of the gastrointestinal tract, perforation or bleedings may occur during the use of NSAIDs at any time both in the presence of alerting symptoms or information about a history

of serious gastrointestinal complications and in the absence of these signs. The consequences of these complications on the whole are more serious in elderly persons.

The use of MOVALIS may be associated with the development of such serious reactions of the skin as exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis. Therefore particular emphasis should be given to the patients who report the development adverse events with respect to the skin and mucosae as well as reactions of hypersensitivity to the product, especially if such reactions were observed during the previous courses of treatment. The development of such reactions is as a rule observed within the first month of treatment. When the first signs of skin rash, changes of mucosae or other signs of hypersensitivity appear, the discontinuation of MOVALIS should be considered.

Cases of an increase of the risk of developing serious cardiovascular thromboses, myocardial infarction, an attack of angina pectoris, possibly with fatal outcome are described during the use of NSAIDs. Such risk increases during a long-term use of the product, and also in patients with a history of the above diseases and predisposed to such diseases.

NSAIDs inhibit in the kidneys synthesis of prostaglandins which participate in maintenance of renal perfusion. The use of NSAIDs in patients with decreased renal blood flow or reduced volume of the circulating blood may lead to decompensation of latent renal insufficiency. After discontinuation of NSAID the renal function usually recovers to the initial level. At the greatest risk of developing such reaction there may be elderly patients, patients with dehydration, congestive heart failure, liver cirrhosis, nephrotic syndrome or acute renal impairment, who concomitantly take diuretics, ACE inhibitors, angiotensin-II receptor antagonists, and also patients who previously had serious surgical interventions leading to hypovolemia. Thorough monitoring of diuresis and renal function should be performed in such patients at the beginning of therapy.

The use of NSAIDs concomitantly with diuretics may result in retention of sodium, potassium and water, and also in a reduction of the natriuretic action of diuretic agents. As a result, the predisposed patients may have an enhancement of symptoms of heart failure or hypertension. Therefore thorough control of the condition of such patients should be performed, and also adequate hydration should be maintained. The study of renal function before the beginning of treatment is necessary. In case of conduction of combined therapy renal function should be also monitored.

An episodic increase of the activity of transaminases in serum or other parameters of renal function may occur during the use of MOVALIS (as well as other NSAIDs). In most cases this increase was slight and transient. If the revealed changes are significant or do not decrease with time, MOVALIS should be discontinued, and the revealed laboratory changes should be monitored.

The weakened or emaciated patients may tolerate worse the adverse events, and for this reason such patients should be under thorough observation.

As with other NSAIDs, MOVALIS may mask symptoms of the basic infectious disease.

As an agent inhibiting cyclooxygenase/prostaglandin synthesis, MOVALIS may influence fertility, and therefore it is not recommended to women with difficulties in conception. In this connection, the women undergoing examination for this reason are recommended to discontinue MOVALIS.

In patients with weak or moderate renal insufficiency (creatinine clearance more than 25 mL/min) no dose adjustment is required.

In patients with liver cirrhosis (compensated) no dose adjustment is required.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The following formulations of Movalis® were previously approved for clinical use in Russian Federation: tablet, suppository, oral suspension, solution for injections. To allow the registration of Movalis capsules, and interchangeability of the safety and efficacy data between Movalis® tablets 15 mg and capsules 15 mg, a local bioequivalence study to assess bioavailability/bioequivalence is deemed to be necessary. If this local trial is successful, marketing authorisation for Movalis® capsules 15 mg will be sought.

Data obtained from phase I trials in healthy male subjects (Trial 107.074 [U93-0094] 107.082 [U93-2038]) conducted in Germany and local regulatory requirements to bioavailability/bioequivalence studies indicate that it is rational to conduct an open-label, single-dose, 2x2 crossover study in general population (healthy male and female volunteers).

Although previous bioavailability/bioequivalence studies on meloxicam were conducted under fed state, it is planned to assess the bioavailability/bioequivalence of Movalis® capsules 15 mg compared to Movalis® tablets 15 mg under fasting state based on these grounds:

- Local bioequivalence studies are conducted at fasting state according to regulatory requirements in Russian Federation [Decision of the Eurasian Economic Commission No. 85, Methodical Guidelines for Conduction of Bioequivalence Studies].
- Pharmacokinetics of meloxicam is not altered by food effect [U88-0771; U93-0260; U98-2348].
- The safety profile of meloxicam is well-known.
- FDA guidance on meloxicam: recommends for conducting bioequivalence studies either under fed state or under fasting state [P12-09147].

The dose (Movalis® capsules 15 mg) selected for the trial is the maximum dose and the same as applied for marketing authorisation in Russian Federation. In accordance the Decision of the Eurasian Economic Commission No. 85 of 03.11.2016 "On Approval of the Rules for Conducting studies of bioequivalence of drugs in the framework of the Eurasian Economic Union"[Decision of the Eurasian Economic Commission No. 85], blood sampling for pharmacokinetics is achieved during 72 hours of each treatment period, separated by wash-out phase of 7 days (about eight half-lives).

2.2 TRIAL OBJECTIVES

2.2.1 Primary objective

The primary objective of the study is to investigate the relative bioavailability of Movalis® capsules 15 mg (Test, T) versus Movalis® tablets 15 mg (Reference, R).

2.2.2 Primary endpoints

Relative bioavailability is primarily to be investigated on the basis of the following pharmacokinetic parameters:

- AUC_{0-t} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to t, the last blood sampling).
  Time frame for the primary endpoint: Baseline (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 32, 48, 72 hours post-dose.

- C_{max} (maximum measured concentration of the analyte in plasma)Time frame for the primary endpoint: Baseline (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 32, 48, 72 hours post-dose.

2.2.3 Secondary objectives

The secondary objectives of the study are:

- To establish bioequivalence of Movalis® capsules 15 mg (Test, T) versus Movalis® tablets 15 mg (Reference, R).
- The assessment of safety and tolerability will be an additional objective of this trial.

2.2.4 Secondary endpoints

The following secondary endpoints will be evaluated.

Pharmacokinetic parameters:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity).
  Time frame for the secondary endpoint: Baseline (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 32, 48, 72 hours post-dose.

2.2.6 Other endpoints

Safety parameters:

- Vital signs (BP, PR, body temperature, respiratory rate)
- Global assessment
- Physical examination
- Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
- 12-lead ECG
- Adverse events

These parameters will be evaluated in a descriptive way only, and are therefore considered to be 'other endpoints'. A confirmatory analysis is not planned (see Section 7.3).

2.3 BENEFIT - RISK ASSESSMENT

Due to the fact that the study is conducted with the participation of healthy volunteers, there is no benefit of drug administration to the state of their health. Volunteers who took part in the study will be provided with monetary compensation for the inconvenience.

However, volunteers as a result of the survey will receive reliable information about their health status (as part of the surveys), as well as information on the individual tolerability of the drugs compared, which may be useful to them in the future

The safety profile of meloxicam is well established from clinical trials and post-marketing surveillance. Eventual adverse events and related cautions and warnings are well known.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to veinipuncture for blood sampling.

The total volume of blood, including blood tests for detecting laboratory abnormalities (general blood analysis, biochemical blood analysis and blood tests for infections (HIV,

hepatitis B, hepatitis C, syphilis)) withdrawn during the entire study per subject will be not more than 253 ml. It does not exceed the volume of a normal blood donation (450 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

Procedure	Quantity	Volume (ml)	Total volume (ml)
Blood chemistry	3	5,0	15,0
General blood analysis	3	5,0	15,0
Serological examination	1	5,0	5,0
PK of meloxicam	32	6,0	192,0
Blood sampling to prevent the heparinized solution from entering the sample	26	1,0	26,0
Total volume, ml	253,0		

Drug-related risks and safety measures

A total of 50 926 patients were treated with meloxicam during the period Aug 1993 – Jun 2010 with a total exposure of 7 932.1 patient-years [U02-0061; U10-2374-01; U09-0192-01; U07-0105; U04-0230; c22930410]. The cumulative estimated exposure of patients to marketed meloxicam during the 1995 – Jun 2010 is estimated at 22 828x10^3 patient years [U10-2374-01]. The review of post-marketing reports for meloxicam till 2011 did not indicate a previously unrecognised medical finding [U02-0061; U10-2374-01; U09-0192-01; U07-0105; U04-0230, U11-1340-01].

The safety data from multiple-dose phase I studies on meloxicam showed a good tolerability at oral doses up to 15 mg in healthy volunteers [U93-0094; U93-2038; U97-2327; U95-2126].

In view of the extensive experience with oral meloxicam in clinical studies and its wide use in therapeutic practice, single oral treatment with meloxicam during each treatment period in the current trial can be accepted to have a highly favourable benefit: risk-profile with a broad safety margin. The available literature data on the clinical use of meloxicam allow one to expect that two single doses of compared drugs do not pose a threat to the life and health of volunteers. For more information please refer to the IB and to the local label.

Possible side effects of meloxicam are described in the Instruction for use of the Movalis® tablets and the Investigator's Brochure, and the investigator will be ready to take all necessary measures to stop them from volunteers. During the study, careful monitoring of volunteers should be made to avoid side effects. In the event that significant clinical symptoms appear in the study, suspicion of their occurrence, it is necessary to urgently conduct a clinical blood test and other necessary studies, as well as take the necessary measures to eliminate.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of alterations in selected liver laboratory parameters to ensure subjects´ safety.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, randomised, single-dose, two-way crossover trial. The two treatment sequences will be randomly allocated to the subjects (Table 3.1: 1).

Table 3.1:1 Summary of treatment sequences

Treatment sequence	Number of subjects per period	Treatment phase	
		Period I	Period II
TR	13	one Movalis® capsule 15 mg (T)	one Movalis® tablet 15 mg (R)
RT	13	one Movalis® tablet 15 mg (R)	one Movalis® capsule 15 mg (T)
Total number of subjects		26	

The treatments will be one Movalis® capsule 15 mg administered under fasting state for T (Test) and one Movalis® tablet 15 mg administered under fasting state for R (Reference). The overall trial scheme is presented in Figure 3.1: 1.

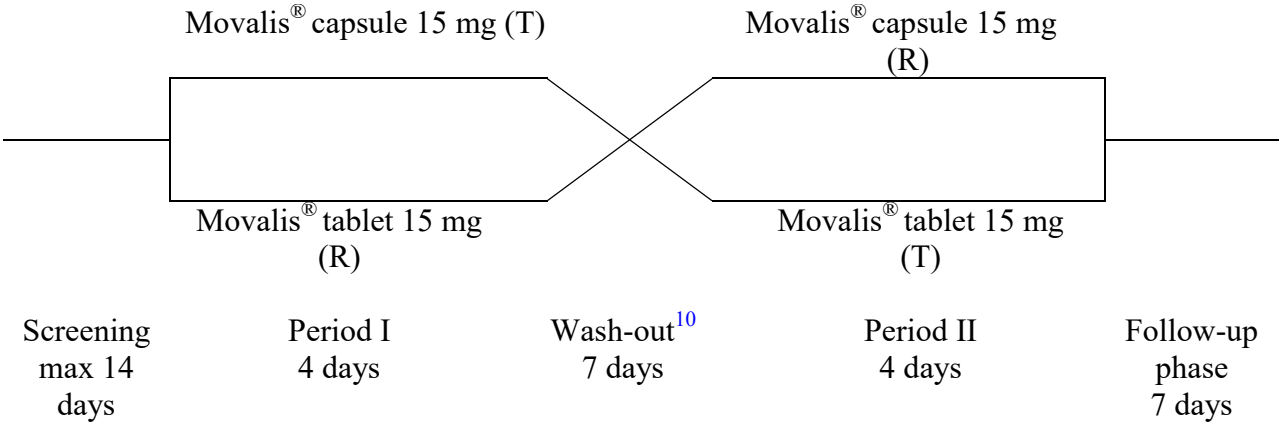

Figure 3.1:1 Trial scheme

[10] The duration of the wash-out period is calculated from the time of administration of the study drug in the first study period to the time of administration of the study drug in the second study period. The interval between the discharge of the study subject from the hospital in the first period and the hospitalization of the study subject in the second study period is about 3.5 days.

Administrative structure of the trial

The trial will be conducted at State budgetary institution of public health in under the supervision of the Principal Investigator.

On-site monitoring will be performed by a contract research organisation appointed by BI.

Safety laboratory tests will be performed by the local laboratory of the trial site.

The trial is sponsored by Boehringer Ingelheim LLC, Russia

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

For bioavailability/bioequivalence study, the crossover design is viewed favourably due to its efficiency: since each subject serves as his/her own control, the comparison between formulations is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between formulations.

3.3 SELECTION OF TRIAL POPULATION

The sample size for this trial was determined assuming an intra-subject coefficient of variation (CV) of 18% for AUC and 23% for C_{max} considering the data reported in the trial 107.074 [U93-0094]. Although intra-subject CV was reported 12.9% for AUC and 17.9% for C_{max}, the data were obtained exclusively from male subjects. Therefore, intra-subject CV assumed for this trial (including male and female subjects) was supposed at least 5% higher than reported previously. Using these CVs and the sample size of 24, the power to conclude bioequivalence is achieved at least 80% if the ratio (both for AUC and C_{max}) is as much as 5% different from the ratio that reflects perfect equivalence (i.e., 100%). Accounting for up to 2 dropouts, 26 subjects will be included in the study.

It is planned that 26 healthy male and female volunteers will be enrolled in the study. Volunteers will be recruited from the volunteers' database of the trial site.

A log of all subjects enrolled into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included into the trial, if they meet the following criteria:

1. Male and female subjects aged 18-45, inclusive.
2. Body mass index by Quetelet between 18.50 -29.99 kg/m2, inclusive.
3. The verified diagnosis is "healthy" according to the conclusion investigator according to the information in the anamnesis, the results of the physical examination, the ECG, the results of measurement of vital signs of the body (blood pressure, heart rate, breathing rate and body temperature), and laboratory indicators.
4. Preconducting standard clinical and laboratory and instrumental studies did not reveal the presence of any diseases and abnormalities.
5. Systolic blood pressure not less than 100 mm Hg. and not higher than 139 mm Hg. diastolic blood pressure not less than 70 mm Hg. and not more than 90 mm Hg. the heart rate is not less than 60 beats per minute and not more than 90 beats per minute, the frequency of respiratory movements is within the range of 12-20 per minute.
6. Ability to understand and accept the explanation of the study; the written informed consent of the volunteer to participate in the study in accordance with applicable law.
7. Female subjects of childbearing potential who agree on using double-barrier contraception from a screening visit to 30 days after the last administration of the study drug, inclusive. If a female is postmenopausal (no menses for at least 1 year) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) she will be exempt from the requirement. In case of using oral contraceptives, these should be withdrawn at least 2 months before the study.
8. Male subjects who agree on using effective contraception (barrier contraceptive methods) from a screening visit to 30 days after the last administration of the study drug, inclusive.

3.3.3 Exclusion criteria

Subjects will not be allowed to participate if any of the following general criteria apply:

1. Drug intolerance of any drug.
2. Allergic history.
3. Acute infectious diseases or allergic reactions requiring treatment (including drug allergy), less than 4 weeks before the screening.

4. Surgical interventions on the gastrointestinal tract (with the exception of appendectomy), which can have a significant effect on the absorption or metabolism of study drugs.
5. Known hypersensitivity to meloxicam or any excipient of the test and reference products.
6. Known hypersensitivity to other NSAIDs: subjects who have developed signs of asthma, nasal polyps, angio-oedema or urticarial following the administration of acetylsalicylic acid or other NSAIDs.
7. Chronic diseases of the cardiovascular, bronchopulmonary, neuroendocrine system, as well as diseases of the gastrointestinal tract, liver, kidneys, blood, or other conditions that make it impossible for the volunteer to participate in the study according to the investigator opinion.
8. The results of standard laboratory and instrumental methods of examination, obtained during the screening, go beyond normal values.
9. History of gastro-intestinal ulceration/ perforation or bleeding; history of malignancy within 5 years before the screening.
10. Positive results of blood tests for infections (HIV, syphilis, hepatitis B or C) at screening.
11. A positive alcohol test at screening.
12. A positive urine drug test (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and amphetamines) at screening.
13. Pregnancy or breastfeeding.
14. Any diet, for example, vegetarian, for 2 weeks before the first day of screening.
15. Alcohol intake more than 10 units. alcohol per week (1 unit of alcohol is equivalent to ½ liter of beer, 200 ml of wine or 50 ml of alcohol) or anamnestic information about alcoholism, drug addiction, abuse of medicines.
16. The inability to be without food for at least 12 hours and the inability to take the drug on an empty stomach.
17. Blood donation (≥ 450 ml) within 3 months before screening.
18. Depot injections, the installation of intrauterine hormonal therapy systems or implants of any drugs for 6 months before the screening;
19. For women: use of hormonal contraceptives less than 2 months before the screening.
20. Regular drug intake within 2 weeks before the screening.
21. Intake of systemic drugs known to alter liver function (barbiturates, omeprazole, cimetidine) within 4 weeks before the screening.
22. For women: volunteers with preserved reproductive potential who had unprotected intercourse with an unsterilized male partner for 30 days before the screening
23. Participation in another clinical trial within 3 months before the screening.
24. Difficult access to the vein, complicating or making it impossible to install a catheter and frequent blood sampling.

25. Smoker (≥10 cigarettes or ≥ 3 pipes per day).
26. Inability to refrain from smoking on study days.
27. Volunteers who do not want or are unable to give up alcohol and excessive physical exertion from the first day of screening and before the visit of follow-up.
28. Volunteers who are unwilling or unable to refuse drinks and food containing methylxanthines (coffee, tea, cola, energy drinks, chocolate, etc.) and grapefruit / grapefruit juice, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) from the first day of screening and until a follow-up visit.
29. Volunteers who lead a lifestyle (including night work and extreme physical activities such as sports or weight lifting), which can make it difficult to interpret the laboratory data obtained during the study.
30. Volunteers who do not intend to comply with the study regime.
31. Volunteers who are obviously or probably, in the opinion of the investigator, are not able to understand and evaluate the information on this study in the process of signing the ICF, in particular regarding the expected risks and possible discomfort.
32. The presence of volunteers dehydration due to diarrhea, vomiting or other cause within the last 24 hours before the first day of screening.
33. The presence of volunteers attacks of seizures, epilepsy and any other neurological disorders in the anamnesis
34. Recent cerebrovascular bleeding or established systemic bleeding disorders.
35. Known lactose intolerance.
36. Reports difficulty for swallowing tablets or capsules.

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent, without the need to justify the decision
2. The investigator decided that the volunteer should be excluded in the interests of the volunteer himself.
3. Non-compliance with the requirements of exclusion criteria, revealed during the study. Deviations of vital signs, as well as standard laboratory and instrumental indicators from the normal values, revealed after the Test or Reference drug intake, are considered as AE.
4. The emergence of AE / SAE, when the continuation of volunteer participation in the study is undesirable or impossible (according to the sponsor or investigator opinion).

5. Vomiting or diarrhea within 12 hours after taking the drug.
6. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication or unauthorized concomitant treatment (protocol violation).
7. Failure to comply with the protocol requirements: the sampling schedule of biosamples (2 times or more), the regime throughout the entire study, including during the washout period, (alcohol consumption, prohibited products, etc.).
8. Non-compliance with the rules of the volunteer stay on a clinical basis.
9. Volunteer receives additional treatment (or needs additional treatment), which can affect the pharmacokinetics of the study drug.
10. The volunteer needs treatment in the hospital during the study.
11. Volunteers enter the hospital after the appointed time (delay more than 1 hour), which violates the protocol requirements.
12. Volunteer has a positive alcohol breath test.
13. Volunteer has a positive pregnancy test.
14. Volunteer has a positive urine drug test (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and amphetamines)
15. Arising side effects of the drug are so serious that the continuation of the study is unacceptable.
16. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to Section 10.1 of this clinical trial protocol and the 'DILI checklist' provided in the ISF.

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). The only exception to this rule is when the subject had an AESI and/or SAE that the investigator considers related to the screening procedure. If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. These discontinuations will be discussed in the CTR.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication has to be stopped immediately, and the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the clinical trial report. For reporting of pregnancy and all related events refer to Section 5.2.2.2.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

3.3.5 Replacement of subjects

Subjects who are enrolled in the trial and do not fulfil the inclusion/exclusion criteria will be replaced and will not receive a randomization number.

In case more than 2 subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study medication is produced by Boehringer Ingelheim. Unit strength of each formulation is based on amount of meloxicam.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

Name:	Movalis®
Substance:	Meloxicam
Pharmaceutical formulation:	Capsule
Pharmaceutical code:	UHAC 62 XX
Source:	Boehringer Ingelheim Ellas A.E., 5th km Paiania – Markopoulo, Koropi Attiki, 19400, Greece.
Unit strength:	15 mg
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	single dose

The characteristics of the reference product are given below:

Name:	Movalis®
Substance:	Meloxicam
Pharmaceutical formulation:	Tablet
Pharmaceutical code:	UHAC 62 XX
Source:	Boehringer Ingelheim Ellas A.E., 5th km Paiania – Markopoulo, Koropi Attiki, 19400, Greece.
Unit strength:	15 mg
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	single dose

4.1.2 Method of assigning subjects to treatment groups

The randomisation list of study subject numbers and assigned treatment sequences will be provided to the trial site in advance.

This trial is an open-label study. The allocation of subjects to one of the two treatment sequences (TR or RT) as per randomisation list will be performed prior to the first study drug administration. For this purpose the subject will be assigned a randomisation number (= random number indicating the treatment sequence) by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject. The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The dose selected for this trial reflects standard clinical doses.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a two-way crossover study. All subjects will receive the two treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4:1 Treatments in a single administration

Treatment	Substance	Formulation	Test or Reference	Total dose [mg]
1	meloxicam	capsule	T	15
2	meloxicam	tablet	R	15

Following an overnight fast of at least 8 hours, the medication will be administered under fasting state as a single oral dose with about 200 mL of ambient boiled water in the sitting/standing position under supervision of two study team members. Subjects will be kept under close medical surveillance until 72 hours following drug administration and are not allowed to lie down during the 2 hours following drug administration. Water is allowed ad libitum except for one hour before drug administration and four hours after drug administration. Standardised meals will be served only at 4, 6, 9 and 11 hours after drug administration.

This trial is a two-way crossover study. All subjects will receive the two treatments in randomised order. The treatments will be separated by a wash-out phase of about eight half-lives (>6 $t_{1/2}$).

The dosage and the method of drug intake is identical to the approved instructions for the use of the original drug Movalis® tablets, as well as to the draft instruction on the use of the reproduced drug Movalis® capsules . Each drug will be taken orally once a day on an empty

stomach by 15 mg (1 tablet/capsule) with an interval between doses (washout period) of at least 7 days (≥6T1 / 2). The dose of drugs does not exceed the average therapeutic dose.

The order of taking the drugs will be determined by the randomization scheme.

Subjects will be kept under close medical surveillance from 10 h before drug administration until 72 h following drug administration. During the first 2 h after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

Not applicable

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by Boehringer Ingelheim. The clinical trial supply consists of containers with trial- and centre identification that hold the trial medication.

Smaller boxes in the clinical trial supply containers will be labelled in Russian according to the legal requirements in Russian Federation.

No re-supply is planned.

Before each dosing, the Test and the Reference drugs will be packed into individual containers for each volunteer to receive in each study period in accordance with the randomization scheme.

Individual containers will be marked with labels that contain the following information:

- Protocol number;
- Name of the test preparation (T / R);
- Study period number;
- Randomization number.

The label composition for labelling individual doses of the study drug and the reference preparation can be supplemented after agreement with the research sponsor.

Label examples are given in the Investigator Site File (ISF).

4.1.7 Storage conditions

Keep drug supplies in their original packaging. Do not store drug supplies at temperature above 25°C.

The trial medication must be stored securely, e.g. in a locked cupboard or at a pharmacy. It may only be dispensed to trial subjects according to the protocol by authorised personnel as documented in the form "Study personal responsibility log".

4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the CRO
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol

Only authorised personnel as documented in the form ‘Study personal responsibility log’ may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor or to the CRO. Receipt, usage and return and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry (‘use-by’) dates. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal or return to the sponsor (and/or) appointed CRO, the investigator / pharmacist / must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator’s possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff.

Standardised meals will be served at the time points described in the Flow Chart.

No food is allowed from 8 h before drug intake until 4 h after drug intake.

No water is allowed from 1 h before drug intake until 4 h after drug intake, except the water administered with the drug and additional 200 mL at 2 h post-dose (mandatory for all subjects). After 4 h post-dose water is allowed ad libitum.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first administration of trial medication until after the last PK sample of each study period is collected.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

Subjects must abstain from smoking and alcoholic beverages for 24 hours prior administration of the study medication and during the treatment phase (Period I and II).

Methylxanthine-containing drinks or foods (coffee, tea, cola, energy drinks, chocolate, etc.), juices of certain fruits (e.g. apples, oranges, grapefruits) are not permitted 24 hours preceeding the administration of study medication and during the treatment phase (Period I and II).

During the treatment phase the subject will receive balanced food of high quality. The standard menu usually includes dietary course without fat and fried food. Meals intake will be controlled and standardised during the treatment phase (Period I and II).

Subjects must use effective methods of contraception (i.e., double-barrier) over the trial period and to 30 days after the last administration of the study drug, inclusive. Women of childbearing potential should practice sexual continence or using barrier contraception methods (non-hormone intrauterine device, condom with intravaginal spermicide, cervical cap with spermicide, diaphragm with spermicide). Women enrolled in the trial are free from obligation to use contraception if they are postmenopausal (absence of menstrual period for at least a year), underwent hysterectomy or tubal ligation, or are confirmed to be infertile.

If a woman becomes pregnant during participation in the trial, she withdraws immediately from the trial. Investigator will fill in a Pregnancy Report Form.

Male subjects participating in the trial must also use effective contraception (barrier contraceptive methods) over the trial period and to 30 days after the last administration of the study drug, inclusive. If a partner of the male subject becomes pregnant, the investigator must be informed about and fill in a Pregnancy Report Form.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety and tolerability of the investigational drug will be assessed based on:

- Vital signs (BP, PR, body temperature, breathing rate)
- Global assessment
- Physical examination
- Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
- 12-lead ECG
- Adverse events (including clinically relevant findings from the physical examination)

These parameters will be evaluated in a descriptive way only, and are therefore considered to be ‘further parameters of interest’. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.2.1 subsections "AE Collection" and "**AE reporting to sponsor and timelines**".

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.2.1 subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which, by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.2.2.

The following are considered as AESIs:

- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

  - an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AEs collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial:
  - All AEs (serious and non-serious) and all AESIs
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the eCRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

The REP for 7 days, when measurable drug levels or PD effects are still likely to be present, is defined as 7 days after the last administration of Meloxicam. Therefore, all AEs that occur through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3. Events that occur after the REP will be considered to be follow-up events.

The follow-up period is the time from the last administration of trial medication, including the REP, until the end of trial examination (last per protocol contact).

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timelines apply as for the initial information.

Information required

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug

exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designate for retests.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

Table 5.2.3: 1 Routine laboratory tests

Category	Test name
Haematology	Erythrocyte sedimentation rate (ESR)
	Haematocrit (Hct) Haemoglobin (Hb) Red Blood Cell Count / Erythrocytes Platelet Count / Thrombocytes
	White Blood Cells / Leucocytes
	Diff Automatic
	Neutrophiles (Relative Count) Eosinophils (Relative Count) Basophils (Relative Count) Monocytes (Relative Count) Lymphocytes (Relative Count)
	Diff Manual (if Diff Automatic is not available)
	Neutrophils, Bands (Stabs) Neutrophils, Polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Clinical Chemistry	Aspartate transaminase (AST) Alanine transaminase (ALT) Alkaline Phosphatase (AP)
	Glucose Creatinine Bilirubin Total Protein, Total Cholesterol, total
	Electrolytes: Calcium, Sodium, Potassium

For haematology and clinical chemistry, 5 ml of blood will be taken per test. A total amount of 35 ml blood will be taken per subject during the trial for safety routine laboratory tests (haematology and clinical chemistry).

Haematology and clinical chemistry is assessed at screening and at 72 h post dose in first and second period.

Table 5.2.3: 2 Routine urinalysis

Category	Test name
Urinalysis (test strips)	Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocyte Urine WBC/Leukocytes Urine pH
Urine-Sediment (microscopic examination) :	Urine Sediment Bacteria Urine Squamous Epith Cells Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes

Urinalysis and Urine-Sediment (microscopic examination) will be assessed at screening and at 72 h post dose in first and second period.

The tests listed in Table 5.2.3: 3 constitute exclusionary lab safety tests. These tests will be performed for eligibility control. The results will not be part of the report.

Table 5.2.3: 3 Exclusionary laboratory tests

Category	Test name
Infectious Serology	Hepatitis B Surface Antigen (qualitative HbsAg test) Hepatitis C Antibodies (qualitative anti-HCV total) HIV-1 and HIV -2 Antibody (qualitative anti-HIV1/2) RPR test for syphilis (Rapid plasma reagin test)
Pregnancy testing (women)	Urine test for ß-HCG (test strips)
Drug Screening (Urine test strips)	Cannabis Benzodiazepines Barbiturates Opiates Cocaine Amphetamines
Alcohol testing	Alcohol breath test (using Alcotester)

Testing for infections (infectious serology) is done at screening.

Pregnancy testing, urine drug tests and alcohol testing will be assessed using express tests at screening and on the hospitalization day of each treatment period.

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded at screening and the time points given in the Flow Chart.

All ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 10 min in a supine position. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Vital signs will be measured at screening and the time points given in the Flow Chart.

Systolic and diastolic blood pressure as well as pulse rate (by palpation, count for 1 minute) will be measured after 10 minutes of rest in the supine/sitting position. All recordings shall be made on the same arm.

Additional vital sign to be recorded is body temperature and breathing rate.

5.2.5.2 Medical examinations

The subject will undergo an assessment of major body systems at screening and the time points given in the Flow Chart.

Body system and site
Skin, hear, nails
Endocrine system
Ear, nose, throat
Cardiovascular system
Gastrointestinal system
Neurological system
Musculoskeletal system
Reproductive system
Renal system

5.2.5.3 Local tolerability

Not applicable

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

Not applicable.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine pharmacokinetic parameters in an appropriate way.

The pharmacokinetic parameters and measurements are generally used as measurements to assess drug exposure.

The scheduled measurements are appropriate to see drug induced changes in vital signs and standard laboratory values. These primary and secondary endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in this kind of studies.

Therefore, the appropriateness of all measurements applied in this trial is given.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and exact clock time of administration as well as of pharmacokinetic sampling times have to be recorded. These actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for meloxicam:

- AUC_{0-t} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for meloxicam:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

A total amount of 192 ml blood will be taken per subject during the whole course of the study for pharmacokinetic purposes.

For quantification of analyte plasma concentrations, 6 mL of blood will be taken from a forearm vein in an K_2EDTA (K_2-ethylendiaminetetraacetic acid)-anticoagulant blood-drawing tube at the following time points:

Table 5.5.2.1: 1 Plasma sampling schedule

Day	Planned Time points in period I
1	-2:00, 0:30, 1:00, 2:00, 3:00, 4:00, 5:00, 6:00, 7:00, 8:00, 10:00, 12:00 h after dosing
2-4	24:00, 32:00, 48:00 and 72:00h after dosing on Day 1

Day	Planned Time points period II
8	-2:00, 0:30, 1:00, 2:00, 3:00, 4:00, 5:00, 6:00, 7:00, 8:00, 10:00, 12:00 h after dosing
9-11	24:00, 32:00, 48:00 and 72:00h after dosing on Day 8

The K2 EDTA-anticoagulated blood samples will be centrifuged no later than 30 minutes after blood sampling. Centrifugation will last for about 10 minutes at 2000g at temperature +4C^{o}. Two aliquots of K2 EDTA plasma samples will be obtained. Both aliquots should contain at least 1.0 ml plasma. Both aliquots should be frozen no later than 30 minutes after the aliquoting. Until shipment on dry ice to the analytical laboratory, the plasma samples will be stored at –20°C or below at the clinical site and at the analytical laboratory until analysis.

The second aliquot will be stored at –20°C or below at the trial site until the clinical trial report is final or shipment is requested by the analytical laboratory.

5.5.2.2 Urine sampling for pharmacokinetic analysis

Not applicable

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

Plasma levels of meloxicam will be determined by a validated HPLC-MS/MS assay (high performance liquid chromatography, tandem mass spectrometry).

5.5.3.2 The bioanalytical method will be documented before the start of the study (preliminary validation) for the subsequent development of the validation report.

The lower limit of quantification (LLQ, LLOQ) of meloxicam will be no more than 0.05 ng/mL, with meeting the condition that the lower limit of quantification will not exceed 5% of the maximum concentration (C_{max}). [P07-08427, P07-07106]

The upper limit of quantification (ULQ, ULOQ) meloxicam will be set up to the linearity of the LC/MS/MS method. Dilution integrity will be validated if necessary to cover the concentration range in the Study samples. Evaluation of dilution integrity may be covered by partial validation.

The validation of HPLC-MS/MS method includes the following parameters:

- ✓ selectivity;
- ✓ linearity;
- ✓ lower limit of quantification (LLQ);
- ✓ calibration range;
- ✓ inter-run and intra-run precision and accuracy;
- ✓ effect of previous sample transfer;
- ✓ extraction degree;
- ✓ effect of the matrix;
- ✓ stability.

Test procedure

The samples will be analyzed in analytical runs. In one run, the following set of samples will be analyzed:

a) Zero (blank) sample, zero sample with the internal standard, not less than 8 points of the calibration curve with a concentration different from zero.

b) Quality control (QC) samples at three concentrations (low, medium, and high), in two replicates for each concentration.

c) Plasma samples of one or more volunteers obtained in two periods.

Determination of analyte concentrations

The analyte concentration in plasma will be calculated using the following equation:

$x = (y – a)/b$

and using the following calibration curve: $y = a + b\,x$, *where:*

- ✓ y is the ratio of the analyte peak to the internal standard peak,
- ✓ x is the concentration of the analyte in plasma,
- ✓ a is the intersection point,
- ✓ b is the slope corresponding to the calibration curve of each analytical run.

The a and b values will be obtained by weighted regression of the calibration curve of each run. The weighted linear regression method will be used because of the wide calibration range.

Values beyond the lower limit of quantification (LLQ) will be considered as zero values.

The calculated concentrations of the calibration samples, quality control (QC) samples, the intersection point, the slope, the correlation coefficient for each analytical run will be presented in the study report in the form of a table.

Acceptability/unacceptability criteria

To assess the acceptability of each analytical run, criteria will be used meeting the following regulatory standards:

- ✓ Guidelines on Expertise of Medicinal Products/edited by of Medicine, . Federal State Budgetary Institution “National Center for Expertise of Medicinal Products”, 2014;
- ✓ Guidance for Industry: Bioanalytical Method Validation (FDA, 2001);
- ✓ Guideline on bioanalytical method validation (EMEA, 2011).

Unacceptability of the entire analytical run

All samples will be analyzed once. The analytical run will be analyzed again if at least one of the below criteria is not met:

- ✓ The calibration curve should include at least 6 points with a non-zero concentration.
- ✓ At least 75% of the calibration samples should meet the following criteria: the concentration of the LLQ sample should be within ±20% of the nominal value, the concentration of the remaining calibration samples should be within ±15% of the nominal value.
- ✓ The concentration values of the control (QC) samples should be within ±15% of the nominal value for at least 67% of the samples (4 of 6). The control samples beyond this interval should not have the same concentration.

Repeated analysis of samples

Some samples will be analyzed again if at least one of the following criteria is met:

- ✓ The concentration of the test sample exceeds the upper limit of quantification (ULOQ). Such sample will be diluted with intact plasma and analyzed again.
- ✓ Insufficient signal from the internal standard.
- ✓ Error during the sample preparation.
- ✓ Inaccurate injection of the sample into the chromatographic system or malfunction of the equipment.
- ✓ Low-quality chromatography.
- ✓ Quantification of the analyte level in a plasma sample obtained before taking the drug by a volunteer.

Some samples collected for repeated analysis and obtained after taking the drug, will be analyzed once. The values obtained during the repeated analysis will be considered the first valid values.

In case of quantitative determination of the analyte level in a plasma sample obtained before taking the drug, the samples will be analyzed twice. A report will be provided on the baseline values, results of the repeated tests, the final result and a conclusion on the acceptability or unacceptability for inclusion in the statistical analysis.

Samples collected for repeated analysis will be analyzed in one analytical run, including samples for constructing a calibration curve and control (QC) samples.

Repeated analysis due to pharmacokinetic reasons is generally not performed; however, repeated analysis can be performed as part of the laboratory study to clarify the possible reasons for obtaining the results assessed as incorrect.

All repeated tests will be performed in accordance with the standard operating procedures of the laboratory. Detailed information on the analysis procedure and validation of results will be included in the final study report.

Incurred Sample Reanalysis (ISR) demonstrates the repeatability and stability of the analytical method in the matrix of real samples. If the number of samples is less than 1,000, about 10% of the samples will be analyzed again; if the number of samples is more than 1,000, the number of re-analyzed samples will be 10% of 1,000 samples and 5% of the number of samples exceeding 1,000. The total number of ISR samples planned for the bioequivalence study will be selected from each volunteer included in the bioequivalence assessment. The ISR will contain samples in the C_{max} range and in the elimination phase.

If the ISR results for a sample are invalid for analytical reasons (a low internal standard zone, sample processing errors, malfunctioning of the measuring equipment), this sample will be excluded from the statistical ISR evaluation and will not be analyzed again. If the number of ISR samples with an invalid analytical result exceeds 5% of all ISR samples, the samples will be analyzed again.

Criterion for the ISR results acceptance: the concentrations obtained from the initial analysis and from the repeated analysis should be within 20% of the average value, for at least 67% of the repeats. If the ISR results are unsatisfactory, the Study Director will decide to investigate the cause of the differences and take adequate measures to minimize the error (and inaccuracy). The ISR results will be presented in the analytical report; they will not be used for any correction of the concentration results for the pharmacokinetic and statistical evaluation of the study

Based on the data on the analyte concentration in the blood plasma of volunteers at discrete time intervals, pharmacokinetic curves (of the concentration dependence on time) will be constructed and pharmacokinetic parameters calculated.

Detailed information on the analysis procedure and validation of results will be included in the final study report.

The analytical work and its documentation can be evaluated by the Sponsor during the monitoring activities. During sample analysis, the bioanalyst will be blinded to subject allocation and will have no access to the random code.

5.5.3.3 Analytical determination of analyte urine concentration

Not applicable

5.6 BIOMARKER(S)

Not applicable

5.6.1 Biochemical and cellular biomarker(s)

Not applicable

5.6.2 Pharmacogenomic biomarker(s)

Not applicable

5.6.3 Methods of sample collection

Not applicable

5.6.4 Analytical determinations

Not applicable

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Time windows are permitted as follows:

Procedures at screening: within 14 days prior to the first study day.

Wash-out phase: 7 days starting from the first drug intake.

End-of-study evaluation: 7 days following the last trial procedure.

For planned individual plasma concentration sampling times refer to the Flow Chart. Sampling time is related to the time of drug administration. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

Deviations from time of sampling are permitted for pharmacokinetic blood sampling as follows:

0 – 2 h: 2 minutes

3 – 6 h: 5 minutes

7 – 12 h: 10 minutes

>12 h: 15 minutes

For other parameters (vital signs, ECG, haematology, clinical chemistry), a time window of ±1 hour is permitted.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

After the volunteers have been informed on the trial, volunteers will sign the written informed consent in accordance with GCP and the local legislation prior to admission to the study.

The subjects will be assigned a screening number and undergo screening. The screening investigations must be completed within 14 days preceding the first study drug administration.

The screening procedures are necessary to determine the subject eligibility to the trial and are outlined in the Flow Chart. The screening includes the following procedures:

- Questioning on demography;
- Questioning on medical history (including lifestyle and bad habits);
- Questioning on prior medication;
- Body weight, height, calculation of body mass index (BMI);

- Assessment of vital signs: blood pressure (BP), pulse rate (PR), body temperature, respiratory rate;
- Physical examination;
- Assessment of exclusionary testing: infectious serology, urine pregnancy test, urine drug screening, alcohol breath test;
- Assessment of routine laboratory tests at fasted state (haematology, clinical chemistry, urinalysis);
- 12-lead ECG (If 12-lead ECG is taken on Day -7-1 at screening, the results can be also used on Day 1 in Period I);
- Evaluation of inclusion / exclusion criteria in the study;
- Assessment of adverse events.

A screening log, including screening number, initials, date of birth and subsequent reason(s) for exclusion from the study, will be completed for all subjects who have given written informed consent.

6.2.2 Treatment period

Each subject will have two periods of 4 days in the treatment phase. Test and reference drug administration will be separated by 7 days (about eight half-lives). For each period the subjects will come to the trial site no later than 10 hours before the planned time the study drug administration and will be confined there at least 72 hours after the study drug administration (Day -1 to 3 in period I and Day 7 to 10 in period II).

The procedures and measurements performed during each treatment period are outlined in the Flow Chart.

In general, if several measurements including venepuncture are scheduled for the same point of time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiologic parameters.

Period I/ Visit 2

Day -1

Hospitalization of the study subjects will be performed not less than 10 hours before the planned time of study drug administration.

After completion of hospitalization, but before randomization, the following procedures will be done:

- Physical examination
- Assessment of adverse events.
- Accounting for concomitant medications
- Evaluation of the change in anamnestic data.
- Evaluation of adherence to the study restrictions.

- Assessment of exclusionary testing using express tests: urine pregnancy test (women), urine drug screening, alcohol breath test.
- Assessment of vital signs: BP, PR, body temperature and respiratory rate;
- 12-lead ECG (If 12-lead ECG is taken on Day -7-1 at screening, the results can be also used on Day 1 in Period I)
- Global assessment
- Evaluation of inclusion / exclusion criteria.

The randomization will be conducted on day -1, after completion of all planned procedures. The randomization numbers will be assigned sequentially in ascending order. The randomization number is assigned to the study subjects for the entire study.

Day 1

Time point from 2 hours before administration to 1 minute before administration:

- Pre-dose blood sampling for PK;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Accounting for concomitant medications.

Time point 00:00:

- The study drug (capsule or tablet) will be taken with 200 ml ambient boiled water in a sitting/standing position under fasting state.

Time point 00:30±0:02 minutes:

- Blood sampling for PK.

Time point 01:00±0:02 minutes:

- Blood sampling for PK.

Time point 02:00±0:02 minutes:

- Blood sampling for PK.

Time point 03:00±0:05 minutes:

- Blood sampling for PK.

Time point 04:00±0:05 minutes:

- Blood sampling for PK;
- Breakfast.

Time point 05:00±0:05 minutes:

- Blood sampling for PK.

Time point 06:00±0:05 minutes:

- Blood sampling for PK;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Dinner;
- Accounting for concomitant medications.

Time point 07:00±0:10 minutes:

- Blood sampling for PK.

Time point 08:00±0:10 minutes:

- Blood sampling for PK.

Time point 09:00:

- Afternoon snack.

Time point 10:00±0:10 minutes:

- Blood sampling for PK.

Time point 11:00:

- Dinner.

Time point 12:00±0:10 minutes:

- Blood sampling for PK;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Accounting for concomitant medications.

Day 2

Time point 24:00±0:15 minutes:

- Blood sampling for PK;
- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Global assessment;
- Assessment of adverse events;
- Accounting for concomitant medications.

Time point 32:00±0:15 minutes:

- Blood sampling for PK;

Day 3

Time point 48:00±0:15 minutes:

- Blood sampling for PK;
- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Global assessment;
- Assessment of adverse events;
- Accounting for concomitant medications.

Day 4

Time point 72:00±0:15 minutes:

- Blood sampling for PK;
- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Global assessment;
- Assessment of adverse events;
- Accounting for concomitant medications.
- Routine laboratory tests (haematology, clinical chemistry, urinalysis);

Standardised meals (breakfast) will be given to subjects at appointed time at the trial site.

All abnormal values (including laboratory parameters) will be registered as AE.

Period II/ Visit 3

Day 7

Hospitalization of the study subjects will be performed not less than 10 hours before the planned time of study drug administration.

After completion of hospitalization, the following procedures will be done:

- Physical examination
- Assessment of adverse events.
- Accounting for concomitant medications
- Evaluation of the change in anamnestic data.
- Evaluation of adherence to the study restrictions.
- Assessment of exclusionary testing using express tests: urine pregnancy test (women), urine drug screening, alcohol breath test.
- Assessment of vital signs: BP, PR, body temperature and respiratory rate;
- 12-lead ECG (If 12-lead ECG is taken on Day -7-1 at screening, the results can be also used on Day 1 in Period I)
- Global assessment

Day 8

Time point from 2 hours before administration to 1 minute before administration:

- Pre-dose blood sampling for PK;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Accounting for concomitant medications.

Time point 00:00:

- The study drug (capsule or tablet) will be taken with 200 ml ambient boiled water in a sitting/standing position under fasting state.

Time point 00:30±0:02 minutes:

- Blood sampling for PK.

Time point 01:00±0:02 minutes:

- Blood sampling for PK.

Time point 02:00±0:02 minutes:

- Blood sampling for PK.

Time point 03:00±0:05 minutes:

- Blood sampling for PK.

Time point 04:00±0:05 minutes:

- Blood sampling for PK;
- Breakfast.

Time point 05:00±0:05 minutes:

- Blood sampling for PK.

Time point 06:00±0:05 minutes:

- Blood sampling for PK;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Dinner;
- Accounting for concomitant medications.

Time point 07:00±0:10 minutes:

- Blood sampling for PK.

Time point 08:00±0:10 minutes:

- Blood sampling for PK.

Time point 09:00:

- Afternoon snack.

Time point 10:00±0:10 minutes:

- Blood sampling for PK.

Time point 11:00:

- Dinner.

Time point 12:00±0:10 minutes:

- Blood sampling for PK;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Accounting for concomitant medications.

Day 9

Time point 24:00±0:15 minutes:

- Blood sampling for PK;
- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Global assessment;
- Assessment of adverse events;
- Accounting for concomitant medications.

Time point 32:00±0:15 minutes:

- Blood sampling for PK;

Day10

Time point 48:00±0:15 minutes:

- Blood sampling for PK;
- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Global assessment;
- Assessment of adverse events;
- Accounting for concomitant medications.

Day 11

Time point 72:00±0:15 minutes:

- Blood sampling for PK;
- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Global assessment;
- Assessment of adverse events;
- Accounting for concomitant medications;
- Routine laboratory tests (haematology, clinical chemistry, urinalysis).
- 12-lead ECG

Standardised meals (breakfast) will be given to subjects at appointed time at the trial site.

All abnormal values (including laboratory parameters) will be registered as AE.

6.2.3 End of trial and follow-up period

Upon completion of the treatment phase, a follow-up phase will be organised for 7 days after the last procedure of period II.

During follow-up visit (Day 18) the following procedures will be done:

- Physical examination;
- Assessment of vital signs (BP, PR, body temperature, respiratory rate);
- Assessment of adverse events;
- Accounting for concomitant medications.
- Urine pregnancy test

In the case of discontinuation, a follow-up will be done 7 days after the last procedure before discontinuation.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The study will be conducted according to an open-label, randomised, single-dose, two-way crossover design. To show bioequivalence, the crossover design is viewed favourably due to its efficiency: since each subject serves as his/her own control, the comparison between formulations is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between formulations.

7.1.1 Objectives

The primary objective is to investigate the relative bioavailability of Movalis® capsules 15 mg versus Movalis® tablets 15 mg following single oral administration in healthy male and female volunteers under fasting state. Movalis® capsule 15 mg is regarded as the test treatment (T) while Movalis® tablet 15 mg is the reference treatment (R). This objective is accomplished by comparing treatments T and R within each subject.

The secondary objectives of the study are:

- To establish bioequivalence of Movalis® capsules 15 mg (Test, T) versus Movalis® tablets 15 mg (Reference, R).
- The assessment of safety and tolerability will be an additional objective of this trial.

7.1.2 Endpoints

Relative bioavailability is primarily to be determined on the basis of the parameters: AUC_{0-t} and C_{max}.

The derivation of these primary parameters is given below.

Additionally, the following PK parameters will also be estimated: $AUC_{0-\infty,}$

The derivation of these other PK parameters is given in Section 7.1.3.

Safety and tolerability will be assessed in a descriptive manner.

7.1.3 Model

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

AUCs: The areas under the curve spanning various time intervals will be calculated using the linear up/log down algorithm. If a drug concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the drug concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_2 \geq C_1$):

The area of the trapezoid between the two data points (t_1, C_1) and (t_2, C_2) will be computed by:

$$AUC_{t1-t2} = 0.5 \times (t_2 - t_1) \times (C_1 + C_2)$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_2 < C_1$):

The area of the trapezoid between the two data points (t_1, C_1) and (t_2, C_2) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_2 - C_1)}{\ln(C_2 / C_1)}$$

$AUC_{0-\infty}$: The area under the plasma concentration-time curve over the time interval from 0 extrapolated to infinity will be calculated according to the following equation

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C'_{tz}}{Kel}$$

where C'_{tz} is the predicted concentration at the time t_z (last time point with a plasma concentration above the quantification limit) at which quantification was still possible. The area under the concentration-time curve from the time point 0 until the last quantifiable drug plasma concentration (AUC_{0-t}) will be calculated by the linear up/log down method as described above.

The pharmacokinetic parameter AUC_{0-t} will be used for testing bioequivalence between Test and Reference formulation [Decision of the Eurasian Economic Commission No. 85].

AUC_{res}: Residual area under the curve will be calculated according to the following equation

$$AUC_{res} = \frac{AUC_{(0-\infty)} - AUC_{(0-t)}}{AUC_{(0-\infty)}}$$

C_{max}: Individual C_{max} values will be directly determined from the plasma concentration time profiles of each subject.

The statistical model used for the analysis of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, where

y_{ijkm} = logarithm of response (AUC_{0-t}, C_{max}, $AUC_{0-\infty}$) measured on subject *m* in sequence *i* receiving treatment *k* in period *j*,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, $i = 1, 2$,

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, $m = 1, 2, ..., n_i$

π_j = the j^{th} period effect, $j = 1, 2$,

τ_k = the k^{th} treatment effect, $k = 1, 2$,

e_{ijkm} = the random error associated with the m^{th} subject in sequence *i* who received treatment *k* in period *j*.

t_{max}: Individual t_{max} values will be directly determined from the plasma concentration time profiles of each subject. If the same C_{max} concentration occurs at different time points, tmax is assigned to the first occurrence of C_{max}.

$t_{1/2}$: The terminal half-life will be calculated from the terminal rate constant using the equation.

$$t_{1/2} = \frac{\ln 2}{Kel}$$

Estimation of k_{el}: The apparent terminal rate constant k_{el} will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles. The log-linear profiles, which include the regression line through the terminal points, will be checked via visual inspection, and it will be determined whether the regression appropriately represents the terminal slope. Only data points that describe the terminal log-linear decline will be included in the regression. A minimum of three points will be used in the determination of k_{el}. If the last concentration-time point increases, this time point may be included if the $t_{1/2}$estimate is reasonable. If k_{el} is not determinable then consequently only parameters not requiring k_{el} will be reported. In addition, the lower ($t_{kz,start}$) and upper ($t_{kz,end}$) limit on time for values to be included in the calculation of k_{el} will be listed.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of Movalis® capsules 15 mg compared to Movalis® tablets 15 mg will be investigated by applying the average bioequivalence method to the ratio between PK parameters AUC_{0-t} and C_{max}.

Bioequivalence of Movalis® capsules 15 mg compared to Movalis® tablets 15 mg is established by using the average bioequivalence method to assess whether the ratio of PK parameters (AUC_{0-t} and C_{max}) of the two treatments (T/R) is contained within a pre-specified acceptance range. Acceptance range for the ratio of geometric means is 80-125% for AUC_{0-t} and 80-125% for C_{max} [Decision of the Eurasian Economic Commission No. 85].

In general, the hypothesis of inequivalence is tested: Null hypothesis H_0 (Inequivalence):

$$\mu_T - \mu_R \leq -\delta \quad \text{or} \quad \mu_T - \mu_R \geq \delta$$

(i.e. the difference of the population average responses is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range),

Alternative hypothesis H_a (Equivalence):

$$-\delta < \mu_T - \mu_R < \delta$$

(i.e. the difference of the population average responses is both greater than the lower bound and less than the upper bound of the acceptance range),where

μ_T and μ_R are the population average responses of the log-transformed measures for the formulations Test (Movalis® capsules 15 mg) and Reference (Movalis® tablets 15 mg),

And δ is the bioequivalence limit that defines the acceptance range for AUC_{0-t} and C_{max} on the logarithmic scale.

In this trial, for example, δ is taken to be ln(1.25) for AUC comparison. This translates to an acceptance range of 80 to 125% for the geometric mean of the ratio of the parameters on the original scale.

This hypothesis and its alternative can be decomposed into two one-sided null hypotheses, H_{01} and H_{02}, with their accompanying alternatives:

H_{01}: $\mu_T - \mu_R \leq -\delta$ vs. H_{a1}: $\mu_T - \mu_R > -\delta$

H_{02}: $\mu_T - \mu_R \geq \delta$ vs. H_{a2}: $\mu_T - \mu_R < \delta$

Due to the nature of normal-theory confidence intervals, the test of the null hypothesis at the $\alpha = 0.05$ level is equivalent to carrying out two one-sided tests of the above null hypotheses each at the $\alpha = 0.05$ level of significance. The rejection of both null hypotheses H_{01} and H_{02} at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary pharmacokinetic parameters will be obtained by non-compartmental analysis using WinNonlin software (Pharsight, USA).

The pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) will be log transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimate and 90% confidence interval for each endpoint.

All evaluable subjects for both treatment periods will be included in the analysis of the relative bioavailability.

A subject is considered to be not evaluable, if:

- The subject has a protocol deviation relevant to the evaluation of relative bioavailability. (Whether a protocol deviation is relevant, will be decided no later than the Report Planning Meeting) or
- The subject experiences emesis and vomiting occurs at or before two times median $t_{max,}$ namely, within 12 hours after study drug administration.

7.3.2 Secondary analyses

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report.

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for plasma concentrations as well as for all primary, secondary and further pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.3.3 Safety analyses

All subjects who received at least one dose of study drug will be included in the safety evaluation. Safety analyses will be performed in accordance with BI standards.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). Adverse events occurring prior to drug administration will be assigned to the screening period while all other adverse events will be assigned to the treatment periods for evaluation.

Independent of this rule, the relationship of an adverse event to the study drugs treatments will be assessed by the investigator. Adverse event information as reported in the CRFs will be aggregated in a two-step process. The evaluation of adverse events will comprise various frequency tabulations.

Descriptive statistics of laboratory values over time for the difference from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.

Safety will also be assessed by evaluation of vital signs (BP, PR, temperature and breathing rate), physical examination, and ECG.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

All randomized volunteers who followed the Protocol requirements, e.g. the volunteers who met the inclusion/exclusion criteria and completed the planned periods of the study drug administration in accordance with all Protocol requirements (except for minor deviations that are not clear grounds for exclusion) constitute a data set “without deviations from Protocol” for the pharmacokinetic assessment.

Data of the following volunteers will be included in the final pharmacokinetic and statistical analysis:

- volunteers who have completed all periods of the study;
- volunteers with missing samples (fewer than two samples).

Calculations will be made on the basis of data on the real, not planned, sampling time of each sample.

The decision to exclude the results of measuring the analyte concentrations in the volunteer samples from analysis will be taken before the final analysis of the samples.

If before taking the test or reference product, a volunteer has a concentration of less than or equal to 5% of the C_{max} value, then the data of this volunteer can be included without any calculations into all pharmacokinetic measurements and calculations. If the concentration value before taking the test or reference product is more than 5% of the C_{max} value, then the data of this volunteer will be excluded from the pharmacokinetic and statistical analysis.

Data of volunteers excluded from the analysis due to the concentration value before the drug dosing higher than 5% of the C_{max} value will be included in a separate appendix of the final study report.

Volunteers, in whose plasma the reference product concentration cannot be determined or is determined in small amounts only, will be excluded from pharmacokinetic and statistical analysis. Concentrations of the analyte in the volunteer are considered very low if his AUC does not exceed 5 percent of the geometrical mean AUC of the reference product (calculated without inclusion of volunteer data with outlying values).

If the LLQ (lower limit of quantification) value is more than 5% of the C_{max} value of an individual volunteer, then the data of this volunteer will be excluded from pharmacokinetic and statistical analysis. The volunteer data are included in a separate appendix of the final study report. During pharmacokinetic and statistical analysis, the drug concentrations below the lower limit of quantification (BLQ) will be counted as zero. Missing samples and non-detectable concentrations (e.g. insufficient amount) from the analytical laboratory will be interpreted in pharmacokinetic analysis as if they were not collected.

7.3.6 Biomarker analysis

Not applicable

7.3.6.1 Analysis of cellular and biochemical biomarkers

Not applicable

7.3.6.2 Pharmacogenomic analyses

Not applicable

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile will be ignored.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.

If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the tables of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.5 RANDOMISATION

Subjects will be randomised to one of the two treatment sequences in a 1:1 ratio. The CRO will arrange for the randomisation scheme (randomization list). The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment is both reproducible and non-predictable. See Section 4.1.2 for the method of assigning subjects to treatment sequences.

Study Sponsor is responsible for the quality of the study drugs, as well as the import into the Russian Federation and the delivery of the IMP in the clinical site.

7.6 DETERMINATION OF SAMPLE SIZE

A sample size for this trial was determined independently using the parameters AUC and C_{max} as a basis for sizing the study.

The sample size for this trial was determined assuming an intra-subject coefficient of variation (CV) of 18% for AUC and 23% for C_{max} considering the data reported in the trial 107.074 [U93-0094]. Although intra-subject CV was reported 12.9% for AUC and 17.9% for C_{max}, the data were obtained exclusively from male subjects. Therefore, intra-subject CV assumed for this trial (including male and female subjects) was considered at least 5% higher than reported previously.

Using CV of 18% for AUC and CV of 23% for C_{max}, and a sample size of 24, the power to reject the null hypothesis of bio-inequivalence for both parameters (AUC and C_{max}) in favour of equivalence at the 5% level of significance is displayed in Tables 7.6: 1 and 7.6: 2 under various assumptions for the intra-subject ratio.

Table 7.6: 1 Probability of concluding equivalence based on AUC (i.e., acceptance range of 80-125%) assuming a coefficient of variation of 18% and various values for the intra-subject ratio, for a two-way crossover (N=24)

Ratio[1]	90%	95%	100%	105%	110%
Power	72%	94%	99%	95%	78%

1) This ratio reflects the median intra-subject ratio defined by exp(μT)/exp(μR) and is estimated by the geometric mean of the intra-subject ratios

Table 7.6: 2 Probability of concluding equivalence based on C_{max} (i.e., acceptance range of 80-125%) assuming a coefficient of variation of 23% and various values for the intra-subject ratio, for a two-way crossover (N=24)

Ratio[1]	90%	95%	100%	105%	110%
Power	54%	81 %	90%	82%	60%

1) This ratio reflects the median intra-subject ratio defined by exp(μT)/exp(μR) and is estimated by the geometric mean of the intra-subject ratios

In accordance with guidelines on conduction of BA/BE studies in Russian Federation, the minimum required number of volunteers is 18 [Methodical Guidelines for Conduction of Bioequivalence Studies]. Assuming 18 participants in the trial, the illustration of probability of concluding equivalence based on AUC and C_{max} is given below (Tables 7.6: 3 and 7.6: 4).

Table 7.6: 3 Probability of concluding equivalence based on AUC (i.e., acceptance range of 80-125%) assuming a coefficient of variation of 18% and various values for the intra-subject ratio, for a two-way crossover (N=18)

Ratio[1]	90%	95%	100%	105%	110%
Power	60%	87%	95%	87%	66%

1) This ratio reflects the median intra-subject ratio defined by exp(μT)/exp(μR) and is estimated by the geometric mean of the intra-subject ratios

Table 7.6: 4 Probability of concluding equivalence based on C_{max} (i.e., acceptance range of 80-125%) assuming a coefficient of variation of 23% and various values for the intra-subject ratio, for a two-way crossover (N=18)

Ratio[1]	90%	95%	100%	105%	110%
Power	43%	67%	76%	68%	48%

1) This ratio reflects the median intra-subject ratio defined by exp(μT)/exp(μR) and is estimated by the geometric mean of the intra-subject ratios

From the above tables (Tables 7.6: 1 and 7.6: 2), a sample size of 24 will have at least 80% power to conclude bioequivalence if the ratio (both for AUC and C_{max}) is as much as 5% different from the ratio that reflects perfect equivalence (i.e., 100%). Accounting for up to 2 dropouts, 26 subjects will be included in the study.

The calculations for single comparisons were performed as described by Diletti et al [R94-1445] using the function power. TOST() of the package PowerTOST Version 1.2-03 in R Version 3.0.3.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki [R10-1167], in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs. Investigators and site staff must adhere to these principles.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF.

8.3 RECORDS

CRF will be approved by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

The investigator must retain a comprehensive and centralised filing system of all study related documentation that is suitable for inspection by the sponsor and representatives of

regulatory authorities until notified by the sponsor, and at least for fifteen years after study completion. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks. /Clinical site will keep archived documents for at least 15 years after the study completion. No study document will be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the sponsor.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

When the trial is completed or terminated, the investigator should inform the IRB, regulatory.

The **start of the trial** is defined as site initiation visit.

The end of the trial is defined as site close out visit.

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment. Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 COMPENSATION AVAILABLE TO THE SUBJECT IN THE EVENT OF TRIAL RELATED INJURY

In accordance with the requirements of the Russian Federation legislation, insurance against the risk of life and health injury is guaranteed to the volunteers participating in the study. The investigator should inform the volunteer about the insurance cover.

The volunteer should be informed that he/she is not allowed to undergo other forms of treatment without the permission of the investigator (except emergency care), and must inform the investigator about any changes in his/her state during participation in the study.

The terms and conditions of this insurance covered in detail are made available to the investigator and the subjects in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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Methodical guidelines for conduction of bioequivalence studies	Ministry of Healthcare and Social Development, Russian Federation, 2008, website.rdg-cro.com/wp-content/uploads/2012/07/Guidelines-for-conducting-bioequivalence-studies-in-Russia.pdf
P12-09147	FDA guidance on meloxicam: recommended bioequivalence studies. 2008.
P07-07106	Yuan Y, Chen X, Zhong D. Determination of meloxicam in human plasma by liquid chromatography-tandem mass spectrometry following transdermal administration. J Chromatogr (B) - Anal Technol Biomed Life Sci 852 (1/2), 650 - 654 (2007)
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R10-1167	WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 59th WMA General Assembly, Seoul, Korea, October 2008.

9.2 UNPUBLISHED REFERENCES

c22930410	Investigator's Brochure: Meloxicam, 107.P0.
U88-0771	et al. Effect of food and antacid (Maalox 70) on pharmacokinetics following single oral administration of UH-AC-62-XX (meloxicam) in healthy volunteers. Trial no. 107.022. Internal study report. 1989-01-31.
U92-0311	and UHAC 62 XX: Efficacy and tolerance of UHAC 62 XX in daily doses of 15, 30 and 60 mg p.o. and piroxicam in a daily dose of 20 mg p.o. in patients with rheumatoid arthritis. Trial no. 107.14. Internal study report. 1991-05-06.

U92-0541 and A three weeks, double-blind, placebo-controlled study to compare the efficacy and safety of three different doses of Meloxicam (7,5 mg, 15 mg, and 30 mg) given once daily in patients with osteoarthritis of the knee. Trial no. 107.42. Internal study report. 1992-04-03.

U93-2016 and A six weeks, double-blind, controlled study to compare the efficacy and safety of two different doses of Meloxicam (15 mg and 30 mg) with Diclofenac sodium sustained release (100 mg) in patients with osteoarthritis of the knee. Trial no. 107.44. Internal study report. 1993-05-28.

U93-2036 and A six months double-blind study to compare the efficacy, safety and tolerance of meloxicam (UHAC-62) and piroxicam in patients with osteoarthritis of the hip or the knee. Trial no. 107.45. Internal study report. 1993-07-26.

U93-0260 et al. Examination of the effect of high fat food on the bio-availability of 15 mg UH-AC 62 XX capsules administered orally to healthy volunteers. Trial no. 107.071. Internal study report. 1992-December.

U93-2066 and A double-blind, placebo-controlled trial to evaluate the efficacy and safety of 15 mg Meloxicam (UH AC 62 XX) once daily per os and 7.5 mg Meloxicam once daily per os in patients with rheumatoid arthritis. Trial no. 107.35. Internal study report. 1993-08-25.

U93-0094 et al. Determination of the relative bioavailability of 15 mg UH-AC 62 XX tablets compared with 15 mg UH-AC 62 XX capsules after oral administration over 7 days to healthy volunteers. Trial no. 107.74. Internal study report. 1992-07-06.

U93-2021 and A six month study to compare the efficacy and tolerance of 15 mg Meloxicam (UHAC 62 XX) capsules and 20 mg Piroxicam capsules in patients with rheumatic arthritis. Trial no. 107.36. Internal study report. 1993-05-28.

U93-2038 et al. Determination of the relative bioavailability of 7.5 mg UH-AC 62 XX tablets q.d. compared with 7.5 mg UH-AC 62 XX capsules q.d. and dose-proportionality between 7.5 mg and 15 mg UH-AC 62 XX capsules q.d. after oral administration over 7 days to healthy volunteers in a three-way cross-over design. Trial no. 107.82. Internal study report. 1993-07-27.

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U98-2348 et al. Influence of a 40 g fat breakfast on the single oral dose pharmacokinetics of the 7.5 mg meloxicam tablet (American type) in healthy subjects: a two-way cross over randomized open study. Trial no. 107.178. Internal study report. 1998-07-02.

U98-3221 et al. A multicenter, double- blind, double-dummy, randomized, parallel-group trial to compare the efficacy and safety of three doses of Meloxicam (3.75, 7.5, and 15 mg) with placebo in patients with osteoarthritis of the knee or hip; and diclofenac (100 mg) as an active control to assess trial sensitivity. Trial no. 107.181. Internal study report. 1998-11-07.

U99-3147 et al. A multicenter, double-blind, double-dummy, randomized, parallel-group trial to compare the efficacy and safety of three doses of meloxicam (7.5, 15 and 22.5 mg) with placebo in patients with rheumatoid arthritis; and with diclofenac (150 mg) as an active control to assess trial sensitivity. Trial no. 107.183. Internal study report. 1999-10-04.

U02-0061 9th Periodic Safety Update report: Meloxicam tablets 7.5 mg, 15 mg, Meloxicam capsules 7.5 mg, 15 mg, Meloxicam suppositories 7.5 mg, 15 mg, Meloxicam capsules 7.5 mg/1.5 mL, 15 mg/1.5 mL, Meloxicam oral suspension 7.5 mg/5 mL (period covered: 14 January 2001 to 13 January 2002). 2002-03-14.

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U07-0105 11th Periodic Safety Update report: Meloxicam tablets 7.5 mg, 15 mg, Meloxicam capsules 7.5 mg, 15 mg, Meloxicam suppositories 7.5 mg, 15 mg, Meloxicam capsules 7.5 mg/1.5 mL, 15 mg/1.5 mL, Meloxicam oral suspension 7.5 mg/5 mL (period covered: 9 November 2004 to 9 July 2007). 2007-09-05.

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-specified AESIs), are to be further evaluated using the following procedures:

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 h. If it is confirmed that ALT and/or AST values ≥3 fold ULN occur in conjunction with an elevation of total bilirubin of ≥2 fold ULN, the laboratory parameters listed below (clinical chemistry, serology, hormones, haematology) must be determined and made available to the investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the 'DILI checklist' provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the 'DILI checklist' provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the 'DILI checklist' provided in the ISF;

and report these via the CRF.

Clinical chemistry

Total protein, glucose, total cholesterol, total bilirubin, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP) electrolytes (Na, K, Ca).

Serology

Hepatitis B Surface Antigen (qualitative HbsAg test); hepatitis C Antibodies (qualitative anti-HCV total); HIV-1 and HIV -2 Antibody (qualitative anti-HIV1/2); RPR test for syphilis (Rapid plasma reagin test).

Haematology

Erythrocyte sedimentation rate (ESR), hematocrit (Hct), haemoglobin (Hb), erythrocytes/ red blood cells (RBC), platelet count, leucocytes/white blood cells (WBC), differential WBC (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then monitor further as specified in the CTP. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

10.2 CONTACT INFORMATION OF THE CRO AND THE CENTRAL LABORATURY

10.2.1 Clinical research organization

Name:

Address:

Study staff:

Full name	Title	Address and contact information
		Address: Telephone: Mobile: E-mail:
		Address: Telephone: Mobile: E-mail:

10.2.2 Local Clinical Laboratory

Name:

Address:

Study staff:

Full name	Title	Address and contact information
		Telephone: Mobile: E-mail:

This laboratory will be used to conduct complete blood count, blood chemistry tests, urinalysis, and urine sediment.

10.2.3 Central Clinical Laboratory

Name:

Address:

Study staff:

Full name	Title	Contact information
		Telephone:

This laboratory will be used to conduct serological tests for HIV, hepatites and syphilis.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c22345272 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: An open-label, randomised, single-dose, two-way crossover study in healthy male and female volunteers to evaluate the relative bioavailability of a new oral formulation of meloxicam, Movalis capsules 15 mg, versus Movalis tablets 15 mg, after administration under fasting state.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor		28 May 2018 13:36 CEST
Approval-Established Core Products		28 May 2018 13:55 CEST
Approval-Team Member Medical Affairs		30 May 2018 13:40 CEST
Author-Trial Statistician		04 Jun 2018 08:38 CEST
Verification-Paper Signature Completion		04 Jun 2018 08:46 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**