Woerwag Pharma LLC

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OBSERVATIONAL STUDY OF EFFECTIVENESS AND SAFETY OF ADD-ON MILGAMMA® AND MILGAMMA® COMPOSITUM STEP-THERAPY IN ROUTINE PRACTICE OF MANAGEMENT OF ADULT PATIENTS WITH ACUTE NON-SPECIFIC LOW BACK PAIN RECEIVING MODERN NSAIDS

Statistical Analysis Plan

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Statistical Analysis Plan is prepared / maintained by trial statistician (CRO "ALMEDIS") and is reviewed / approved by the company Woerwag Pharma LLC.

Prepared by: [redacted] [redacted]

Kristina Bondareva
Sr Statistician
ALMEDIS

Date

Approved by: [redacted] [redacted]

Anna Shagako
Clinical Trials Manager
Woerwag Pharma LLC

Date

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
COX	Cyclooxygenase
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
FAS	Full Analysis Set
IC	Informed Consent
IQR	Interquartile Range
LCL	Lower Confidence Limit
LLT	Low Level Term
LOCF	Last Observation Carried Forward
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mg	Milligram
mL	Milliliter
mm	Millimeter
NA	Not Applicable
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
Q1	First quartile
Q3	Third quartile
SAP	Statistical Analysis Plan
SOC	System Organ Class
SD	Standard Deviation
UCL	Upper Confidence Limit
VAS	Visual Analogue Scale
VCAS	Valid Case Analysis Set
WHO	World Health Organization

1 INTRODUCTION

This is a multi-centre observational (non-interventional) prospective study that is planned to be conducted to assess the effectiveness of neurotropic vitamins therapy with Milgamma®/ Milgamma® compositum in combination with modern NSAIDs (preferential/selective COX-2 inhibitors) in patients with non-specific back pain.

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol.

The following documents were used to create this statistical analysis plan:

- Clinical study protocol (CSP) version 1.0 dated as of December 5th, 2018;
- Case report form (CRF) version 1.1 dated as of March 20th, 2019.

The SAP will be finalized and signed prior to database lock. Revisions to the approved SAP may be made prior to database lock. Revisions will be version controlled.

Any changes from the analyses planned in the SAP will be explained in the Clinical Study Report (CSR).

1.1 Study Synopsis

Study title Observational Study of Effectiveness and Safety of Add-on Milgamma® and Milgamma® compositum Step-Therapy in Routine Practice of Management of Adult Patients With Acute Non-Specific Low Back Pain Receiving Modern NSAIDs	
Sponsor	Woerwag Pharma LLC
National Coordinator	Prof. V.A. Parfenov
Deputy Investigator	
Study Site(s)	Approx. 50 sites (neurologists in outpatient clinics, 1 medical physician = 1 site) Prior to the start of the study, neurologists (potential investigators) will be asked to fill out feasibility questionnaires to identify their individual routine practice regarding prescription or non-prescription of Milgamma® / Milgamma® compositum. Based on results of feasibility physicians will be divided to non-prescribers and prescribers of Milgamma® / Milgamma® compositum to the patients with acute non-specific low back pain. In each medical institution, such non-prescribers and prescribers will be proposed to participate in the study. Non-prescribers will be responsible for enrolling group (1) (NSAIDs alone), prescribers will be responsible for enrolling group (2) (NSAIDs + Milgamma® / Milgamma® compositum).
Study Identification Code	WP-RU-2018/1
Study Phase	Not applicable (NIS)
Study Design	Observational (non-interventional), multicentre, prospective
Rationale	There is still a lack of scientific and clinical data on neurotropic vitamins therapy in combination with modern NSAIDs (preferential/selective COX-2 inhibitors) in patients with non-specific back pain. Currently use of modern NSAIDs has been increased dramatically while traditional NSAIDs are decreasing. In previous clinical and observational studies on acute non-specific back pain only traditional NSAIDs were used. The current observational study will provide unique data on routine practices of management of adult patients with acute non-specific low back pain using modern NSAIDs in Russia and clinical use of Milgamma® and Milgamma® compositum step-therapy in Russian patients with acute low back pain receiving modern NSAIDs in a real life setting. This observational study will allow to clarify the effectiveness and safety of Milgamma® and Milgamma® compositum in Russian patients with acute low back pain. The study results can contribute to optimization of management and improvement of outcomes of this frequent disease by reducing use of NSAIDs that have many side effects.
Indication/ Therapeutic Area	Acute non-specific back pain / Neurology
Investigational product	

Name of Investigational Product	Milgamma® and Milgamma® compositum
Active Ingredient(s)	Millgamma®: Thiamin hydrochloride 100 mg, pyridoxine hydrochloride 100 mg, cyanocobalamin 1 mg, lidocaine hydrochloride 20 mg Milgamma® compositum: benfotiamin 100 mg, pyridoxine hydrochloride 100 mg
Dose and mode of administration	5-10 Injections of Milgamma®, 2 mL injection solution, each. One injection per day, followed by oral administration of Milgamma® compositum, 1 tablet 3 times per day for 4 weeks. Further continuation of treatment according to physician's decision in accordance with the approved Instructions for Medicinal Use for Milgamma® and Milgamma® compositum. Milgamma® and Milgamma® compositum will be used in combination with modern NSAIDs (see comparator treatment), which will be prescribed in accordance with the instructions for medical use and the clinical practice of the physician.
Comparator treatment (NIS)	
Name/ Descript. of reference Product (if applicable)	Modern NSAIDs (preferential/selective COX-2 inhibitors): products with International Nonproprietary Names (INN) celecoxib, etoricoxib, meloxicam, nimesulide.
Active Ingredient (if applicable)	Please refer to the paragraph above.
Dose and mode of administration	NSAIDs will be prescribed in accordance with instruction for medical use and routine practice of the investigator.
Duration of treatment	Patients will be enrolled in one of the two groups depending on the prescribed therapy: (1) Modern NSAIDs (preferential/selective COX-2 inhibitors) (2) Modern NSAIDs (preferential/selective COX-2 inhibitors) + Milgamma® / Milgamma® compositum. Duration of treatment with NSAIDs will be defined in accordance with instructions for medical use and the clinical practice of the physician. For patients in treatment group (2) Milgamma® therapy will be lasted 5-10 days, Milgamma® compositum therapy approximately 4 weeks.
Study period (clinical part)	10 months
Timing (Visits)	Visit 1 (baseline), telephone/on-site visit 2 (after 5 days), visit 3 (after 10 days) telephone/on-site visit 4 (after 24 days), telephone/on-site visit 5 (after 38 days), telephone/on-site visit 6 (after 52 days), telephone/on-site visit 7 (after 66 days), telephone/on-site visit 8 (after 80 days) and telephone/on-site visit 9 after 94 days
Estimated Study Duration	Q4 2018 to Q4 2019
Study Population	Adult out-patients with acute non-specific low back pain who have been prescribed (but have not started yet) therapy consisting of

	(1) modern NSAIDs (2) modern NSAIDs + Milgamma® / Milgamma® compositum
Sample Size	Approximately 500 patients within age group of 18-60 years (both inclusive).
Inclusion Criteria	1. Signed informed consent including data protection declaration according to the local legislation. 2. Female and male outpatients aged 18-60 years (inclusive). 3. Acute non–specific low back pain less than 21 days (= 3 weeks). 4. Low back pain treatment with (1) modern NSAIDs (preferential/selective COX-2 inhibitors) or (2) modern NSAIDs (preferential/selective COX-2 inhibitors) + Milgamma®/ Milgamma® compositum prescribed (but not started yet) in frames of routine medical practice. 5. Prescribed (but not started yet) step-therapy with Milgamma® to be followed by Milgamma® compositum in accordance with locally approved instruction for medical use (for the group planned to be treated with Milgamma®/ Milgamma® compositum step-therapy). 6. Pain intensity according to Numerical Rating Scale (NRS) ≥4 points ≤9 at the time of enrollment. 7. In case of presence of previous episodes of acute non-specific low back pain in medical history, the last one had resolved at least 30 days before the start of current episode.
Exclusion Criteria	1. Intolerance or hypersensitivity to the active ingredients or any excipient(s) of Milgamma®, Milgamma® compositum (for the group prescribed with Milgamma®/ Milgamma® compositum step-therapy) or other acute low back pain treatment received by patient. 2. History or presence of any disease that, in the opinion of the investigator, might confound the results of the study, poses an additional risk to the subject during participation in the study or can change pain perception (examples of such possible conditions: any malignancy, stomach ulcer, duodenal ulcer, chronic heart failure, bronchial asthma, psychiatry disorders, epilepsy, Parkinson Disease etc). 3. Spinal surgery/rehabilitation in the last 12 months. 4. Acute back pain that is attributable to any known or suspected specific identifiable cause (e.g. discogenic radiculopathy, spondylolisthesis, osteomalacia, inflammatory arthritis, metabolic, neurological diseases or tumor). 5. Severe scoliosis. 6. Pregnancy, breast feeding. 7. Severe conduction disturbances or acute

	decompensated cardiac insufficiency (for the group prescribed with Milgamma®/ Milgamma® compositum step-therapy). 8. Use of anticoagulants with increased risk of bleeding and/or formation of hematoma after injection 9. Use of NSAIDs or vitamins B within 2 months prior to enrollment into the study. 10. Necessity to use myorelaxants or antidepressants for treatment of acute non-specific low back pain. 11. Prior use of non-pharmacological treatment (physiotherapy, heat treatment (e.g. heat patch, hot water bottle) or topically applied medicinal products to the back area, procaine blocks) within the last 3 days before study entry. 12. Participation in another clinical or observational study – currently or within 6 months prior to study entry. 13. Legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible impact of the study. 14. Employees of the investigator or the institution who are directly involved in the study or other studies under the direction of the investigator or his/her associates.
Study Objectives	
Primary Objective	Primary objective of the study is to assess the pain reduction in patients with acute non-specific low back pain receiving modern NSAIDs (preferential/selective COX-2 inhibitors) in combination with Milgamma®/ Milgamma® compositum step-therapy in routine medical practice compared to patients receiving modern NSAIDs alone.
Secondary Objective	• To assess pain related disability in patients with acute non-specific low back pain in routine medical practice. • To assess the safety of Milgamma®/ Milgamma® compositum step-therapy in patients with acute non-specific low back pain in routine medical practice. • To assess the patients' prescribed and actual treatment with Milgamma®/ Milgamma® compositum step-therapy. • To assess NSAIDs usage in patients receiving modern NSAIDs (preferential/selective COX-2 inhibitors) with and without Milgamma®/ Milgamma® compositum step-therapy in routine medical practice. • To assess patients' satisfaction with the treatment of acute non-specific low back pain in routine medical practice. • To assess long-term effectiveness of Milgamma®/ Milgamma® compositum step-therapy 3 months after start of treatment in routine medical practice.
Evaluation Criteria (Endpoints)	All endpoints will be compared between therapeutic groups.

Primary Endpoint	Change of pain intensity measured on 0-10 points NRS scale from baseline to 10 days after the start of treatment.
Secondary Endpoints	<u>Effectiveness endpoints:</u> • Change from baseline in pain intensity measured on 0-10 points NRS scale at 5, 24 and 38 days after the start of treatment. • Change from baseline in pain intensity measured on 0-10 points NRS scale over time. • Percentage of patients showing at least 30% relief with respect to pain intensity (as measured on 0-10 points NRS) at 5, 10, 24 and 38 days after the start of treatment. • Change in pain-related disability, measured by Roland Morris disability questionnaire from baseline to 10 days after the start of treatment. • Percentage of patients with at least one pain flare-up registered during 3 months after start of treatment. • Percentage of patients with at least one pain flare-up resulting in consultancy with physician or professional management registered during 3 months after start of treatment. • Percentage of patients with at least one pain flare-up resulting in disruption of daily activity registered during 3 months after start of treatment. • Percentage of patients with at least one pain flare-up resulting in NSAIDs intake registered during 3 months after start of treatment. • Number of treatment days with NSAIDs <u>Patient treatment and patient satisfaction endpoints:</u> • Prescribed and actual number of Milgamma® injections (for the group treated with Milgamma®/ Milgamma® compositum step-therapy). • Prescribed and actual number of treatment days with oral Milgamma® compositum (for the group treated with Milgamma®/ Milgamma® compositum step-therapy). • Patient satisfaction with treatment using a 5-point verbal rating scale after 5, 10, 38 days and 3 months since the start of treatment. • Number and percentage of patients prematurely discontinued prescribed therapy with Milgamma®/ Milgamma® compositum by reasons for discontinuation (for the group treated with Milgamma®/ Milgamma® compositum step-therapy). • Reasons for early discontinuation of study participation.
Safety endpoints	• Frequency and severity of ADRs during the study.
Statistical Methods	The between-group comparison on primary endpoint –

	change from baseline in pain intensity as measured on 0-10 points NRS scale at 10 days after the start of treatment – as well as on changes from baseline in pain intensity at each individual time point and in pain-related disability at 10 days after the start of treatment (secondary endpoints) will be performed using analysis of covariance (ANCOVA) adjusting for baseline value of the corresponding parameter. Inclusion of center effect into the model will also be considered. The analysis of change in pain intensity over time will be performed, using linear mixed model repeated measures with a random effect for subject and fixed effect terms for treatment, visit, treatment-by-visit interaction and baseline pain intensity. The secondary endpoint – percentage of subjects showing at least 30% relief with respect to pain intensity – will be compared between groups using logistic regression with treatment group as fixed factor and baseline pain intensity as a covariate. Percentage of patients with at least one pain flare-up will be compared between groups using Fisher's exact test. Number of days of treatment with NSAIDS will be compared between groups using Wilcoxon–Mann–Whitney test. All comparisons will be conducted at the two-sided level of significance 5%. The results on the study endpoints will also be presented with two-sided 95% confidence intervals, where applicable. Descriptive summaries and listings will be provided for all collected data and derived parameters.

2 FLOW CHART AND VISIT SCHEDULE

TABLE 1 STUDY FLOW CHART

Visits	**Visit 1**	**Visit 2 (Phone call or on-site visit)**	**Visit 3**	**Visit 4 (Phone call or on-site visit)**	**Visit 5 (Phone call or on-site visit)**	**Visit 6 (Phone call or on-site visit)**	**Visit 7 (Phone call or on-site visit)**	**Visit 8 (Phone call or on-site visit)**	**Visit 9 (Phone call or on-site visit)**
Days since the start of therapy	**Day 0 (Therapy is prescribed, but not started yet)**	**Day 5 since the start of therapy**	**Day 10 since the start of therapy**	**Day 24 since the start of therapy**	**Day 38 since the start of therapy**	**Day 52 since the start of therapy**	**Day 66 since the start of therapy**	**Day 80 since the start of therapy**	**Day 94 since the start of therapy**
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics and baseline characteristics	X								
Medical History	X								
Pain intensity – NRS (Numerical Rating Scale)	X	X	X	X	X	X	X	X	X
Pain-related disability (Roland Morris disability questionnaire)	X		X						
Presence of days with pain		X	X	X	X	X	X	X	X
Pain flare-up[1]					X	X	X	X	X
Patient satisfaction with treatment (5-point verbal rating scale)		X	X	X	X				X
Details on LBP treatment with Milgamma®/ Milgamma® compositum (if applicable)	X	X	X	X	X	X	X	X	X
Assessment of medication/ treatment of LBP including NSAIDs	X	X	X	X	X	X	X	X	X
ADR assessment		X	X	X	X	X	X	X	X

1 Pain flare-ups: reappearance of pain after pain-free period lasting approximately 4 weeks, including those resulting in consultancy with physician or professional management, resulting in disruption of daily activity and resulting in NSAIDs intake.

3 STUDY OBJECTIVES

Primary objective of the study is to assess the pain reduction in patients with acute non-specific low back pain receiving modern NSAIDs (preferential/selective COX-2 inhibitors) in combination with Milgamma®/ Milgamma® compositum step-therapy in routine medical practice compared to patients receiving modern NSAIDs alone.

Secondary objectives:

- To assess pain related disability in patients with acute non-specific low back pain in routine medical practice.
- To assess the safety of Milgamma®/ Milgamma® compositum step-therapy in patients with acute non-specific low back pain in routine medical practice.
- To assess the patients' prescribed and actual treatment with Milgamma®/ Milgamma® compositum step-therapy.
- To assess NSAIDs usage in patients receiving modern NSAIDs (preferential/selective COX-2 inhibitors) with and without Milgamma®/ Milgamma® compositum step-therapy in routine medical practice.
- To assess patients' satisfaction with the treatment of acute non-specific low back pain in routine medical practice.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multi-centre observational (non-interventional) prospective non-randomized parallel group study that is planned to be conducted to assess the effectiveness of neurotropic vitamins therapy with Milgamma®/ Milgamma® compositum in combination with modern NSAIDs (preferential/selective COX-2 inhibitors) in patients with non-specific back pain.

4.2 Study Population

Adult out-patients with acute non-specific low back pain who have been prescribed (but have not started yet) therapy consisting of (1) modern NSAIDs (preferential/selective COX-2 inhibitors) or (2) modern NSAIDs (preferential/selective COX-2 inhibitors) + Milgamma® / Milgamma® compositum will be enrolled in the study.
It is planned to enrol approximately 500 patients within age group of 18-60 years.
Only patients, who provide written consent to participate in the study and have been informed by a physician on objectives and methods of this project, will be enrolled in the study.
Each patient should meet all inclusion criteria and none of the exclusion criteria for this study specified in Sections 10.2.1 and 10.2.2 of the Study Protocol, respectively.

4.3 Study Treatment

The responsibility for the treatment of each patient lies solely by the attending physician. Patients will be enrolled in one of the two groups depending on the prescribed therapy:
Group 1 (Reference): Modern NSAIDs (preferential/selective COX-2 inhibitors);
Group 2 (Test): Modern NSAIDs (preferential/selective COX-2 inhibitors) + Milgamma® / Milgamma® compositum.
Modern NSAIDs (preferential/selective COX-2 inhibitors): products with INN celecoxib, etoricoxib, meloxicam, nimesulide. NSAIDs will be prescribed in accordance with instruction for medical use and routine practice of the investigator. Dose and route of administration will be according to instruction for medical use.

Millgamma®: 2 mL injection solution containing thiamin hydrochloride 100 mg, pyridoxine hydrochloride 100 mg, cyanocobalamin 1 mg, lidocaine hydrochloride 20 mg.
Milgamma® compositum: 1 tablet containing benfotiamin 100 mg, pyridoxine hydrochloride 100 mg.
Following doses and modes are used for Milgamma® / Milgamma® compositum in accordance with instruction for medical use:
5-10 Injections of Milgamma®, 2 mL injection solution, each; 1 injection per day, followed by oral administration of Milgamma® compositum; 1 tablet 3 times per day for 4 weeks. Further continuation of treatment according to physician's decision in accordance with the approved Instructions for Medicinal Use for Milgamma® and Milgamma® compositum.

4.4 Efficacy and Safety Endpoints

All effectiveness endpoints will be compared between treatment groups.

4.4.1 Primary Endpoint

The primary effectiveness endpoint is change of pain intensity measured on 0-10 points NRS scale from baseline to 10 days after the start of treatment.

4.4.2 Secondary Endpoints

The secondary effectiveness endpoints are:

- Change from baseline in pain intensity measured on 0-10 points NRS scale at 5, 24 and 38 days after the start of treatment.
- Change from baseline in pain intensity measured on 0-10 points NRS scale over time.
- Percentage of patients showing at least 30% relief with respect to pain intensity (as measured on 0-10 points NRS) at 5, 10, 24 and 38 days after the start of treatment.
- Change in pain-related disability, measured by Roland Morris disability questionnaire from baseline to 10 days after the start of treatment.

- Percentage of patients with at least one pain flare-up registered during 3 months after start of treatment.
- Percentage of patients with at least one pain flare-up resulting in consultancy with physician or professional management registered during 3 months after start of treatment.
- Percentage of patients with at least one pain flare-up resulting in disruption of daily activity registered during 3 months after start of treatment.
- Percentage of patients with at least one pain flare-up resulting in NSAIDs intake registered during 3 months after start of treatment.
- Number of treatment days with NSAIDs

Patient treatment and patient satisfaction secondary endpoints are:

- Prescribed and actual number of Milgamma® injections (for the group treated with Milgamma®/Milgamma® compositum step-therapy).
- Prescribed and actual number of treatment days with oral Milgamma® compositum (for the group treated with Milgamma®/ Milgamma® compositum step-therapy).
- Patient satisfaction with treatment using a 5-point verbal rating scale after 5, 10, 38 days and 3 months since the start of treatment.
- Number and percentage of patients prematurely discontinued prescribed therapy with Milgamma®/Milgamma® compositum by reasons for discontinuation (for the group treated with Milgamma®/Milgamma® compositum step-therapy).
- Reasons for early discontinuation of study participation.

4.4.3 Safety Endpoints

- Frequency and severity of ADRs during the study.

5 STATISTICAL METHODS

5.1 General Considerations

Continuous data will be summarised in terms of the number of observations (n), mean, standard deviation (SD), lower (LCL) and upper (UCL) 95% confidence limits for the mean, first quartile (Q1), median, third quartile (Q3), minimum (Min) and maximum (Max). The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, SD, 95% confidence limits for the mean, median, first quartile and third quartile will be reported to one more decimal place than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarised in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will be calculated using n as the denominator if not specified otherwise.

Confidence intervals will be presented to one more decimal place than the raw data.
All comparisons will be conducted at the two-sided level of significance 5%.

The following visit names will be used:

- Visit 1 (Baseline)
- Visit 2 (Day 5)
- Visit 3 (Day 10)
- Visit 4 (Day 24)
- Visit 5 (Day 38)
- Visit 6 (Day 52)
- Visit 7 (Day 66)
- Visit 8 (Day 80)
- Visit 9 (Day 84)

For presentation of Visit 84 data, the values of patients who discontinued the study early will be ignored.

Baseline value will be defined as measurement obtained at the initial visit (before start of therapy). Changes from baseline at each individual visit will be calculated as (post-baseline-baseline value).

Taking into account the observational nature of the study, the analysis will be performed based on actual treatment received.

Since in this protocol 1 site = 1 physician, and each physician is expected to enroll only a small number of patients (approximately 10) into only one of the two treatment groups, site effect will not be included into the model for the evaluation of any endpoint.

5.2 Study Patients

5.2.1 Disposition of Patients

The following patient disposition summaries will be provided:

- A summary of the number of patients signed informed consent (IC) for the study, number of screen failures, number of subjects included in each of the two treatment groups, number of subjects treated
- A summary of prescribed treatment with modern NSAIDs
- A summary of the number of patients who violated any inclusion/exclusion criterion
- A summary of the number and percentage of patients attended each visit during the study
- A summary of the number and percentage of patients completed the study
- A summary of the number and percentage of discontinuations from the study overall and by major reason

A patient is considered as attended the visit date is available. By-patient listings of inclusion and disposition details, visit dates and withdrawal/study completion details will be provided.

5.2.2 Protocol Deviations

Not Applicable.

5.2.3 Analysis Populations

5.2.3.1 All Patients Set

All Patients Set will be defined as all patients who signed informed consent for entry into the study.

5.2.3.2 Full Analysis Set (FAS)

Full Analysis Set (FAS) will be defined as all patients who signed informed consent for entry into the study, started the study treatment, and provided baseline and at least one post-baseline assessment of at least one effectiveness parameter. FAS will be the primary population for the analysis of effectiveness.

5.2.3.3 Valid Case Analysis Set

Valid Case Analysis Set will be defined as all FAS patients who are eligible (had no inclusion/exclusion criteria violations) and for whom the assessment of the primary variable is available. VCAS will be used for sensitivity analysis of the primary endpoint.

5.2.3.4 Safety Population

Safety Population will be defined as all patients who signed informed consent for entry into the study and started the study treatment. Safety population will be used for the analysis of ADRs.

A summary of the number and percentage of patients in each analysis population will be produced. A by-patient listing of analysis population will be provided.

5.3 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristic summaries will be provided by treatment group and overall:

- A summary of demographic variables (age, age group, gender, height and weight at Visit 1) (Safety Population, Full Analysis Set)
- A summary of information on low back pain: time from start of the current episode (in days), proportion of patients for whom current episode is the first episode of LBP in the anamnesis, time since resolution of the last episode (in months) for patients with recurrent episode. (Safety Population, Full Analysis Set)
- A summary of baseline characteristics: baseline pain, baseline pain-related disability score. (Safety Population, Full Analysis Set)
- A summary of medical history, in terms of body system and preferred term. (Safety Population)
- A summary of previous and concomitant medication for low back pain. (Safety Population)
- A summary of previous and concomitant non-drug treatments for low back pain. (Safety Population)
- A summary of concomitant medications (for the treatment of concomitant diseases) at the time of Visit 1 in terms of ATC class and Lowest Level Term (LLT). (Safety Population)

Age will be calculated as the number of complete years between a patient's birth date and the date of their first visit. Categories of Age group will be as follows: <30, 30-39, 40-49, >=50 complete years.

Time from start of the current episode will be calculated as (date of Visit 1 - current episode start date).
Time from resolution of the last episode (in months) for patients with recurrent episode will be calculated as (current episode start date – last episode resolution date)/ 30.44.

In case if only day of last episode resolution is missing then 15 will be used to impute the day. In case if month is missing the date of last episode resolution will be imputed using July 1st for calculation.

MedDRA, version 21.1 (or later if available at ALMEDIS) will be used for coding adverse drug reactions, medical history events and non-drug treatments. WHO Drug Dictionary (WHO DDE version 15 March 2019 or later if available at ALMEDIS) will be used for coding any prior and concomitant drug therapy.

A by-patient listing of demographic and baseline data will be provided.

5.3.1 Flagging of Concomitant Medications and Non-Drug Treatments as Prior or Concomitant

Medication start and stop dates will be compared to the date of first dose of study medication (infusion start date) to allow medications to be classified as either Prior or Concomitant.
Medications that start and stop prior to the date of first dose of study medication will be classified as Prior medications. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be classified as both Prior and Concomitant unless there is clear evidence that it stopped prior to the first dose of study medication, in which case the medication will be assumed to be Prior.

5.4 Treatment Compliance

Actual treatment duration will be calculated in days as (date of last dose – date of first dose + 1) separately for treatment with Milgamma® and Milgamma® compositum.
Descriptive statistics on treatment duration will be presented for the Safety Population.

A by-patient listing of treatment exposure data will be provided.

5.5 Effectiveness Evaluation

All effectiveness evaluations will be performed for Full Analysis set. Valid Case Analysis set will be used to present sensitivity analysis for the primary endpoint.

5.5.1 Primary Endpoint – Change of pain intensity measured on 0-10 points NRS scale from baseline to 10 days after the start of treatment

Since the superiority of one treatment over the other is investigated and taking into consideration that smaller negative values of the primary variable correspond to the greater reduction of pain in comparison to baseline, the statistical hypotheses for this study are formulated as follows:
Null hypothesis (H_0):
H_0: $\mu 2 - \mu 1 \geq 0$
Alternative hypothesis (H_A):
H_A: $\mu 2 - \mu 1 < 0$, where μ1 и μ2 are the true mean changes from baseline in pain intensity for (1) modern NSAIDs (preferential/selective COX-2 inhibitors) therapy and for (2) modern NSAIDs (preferential/selective COX-2 inhibitors) + Milgamma® / Milgamma® compositum therapy, correspondingly.

The between-group comparison on primary endpoint – change from baseline in pain intensity as measured on 0-10 points NRS scale at 10 days after the start of treatment – will be performed using analysis of covariance (ANCOVA). The difference between pain intensity at 10 days after the start of treatment and baseline (V3-V1) as response variable, treatment group as fixed factor and baseline pain intensity as a covariate will be included into the model.
Mean change from baseline along with 95% confidence interval estimated using the ANCOVA model will be presented by treatment group. The difference of mean change from baseline between groups with 95% CI will also be estimated.

The primary analysis will be performed on the Full Analysis Set. For the primary analysis missing values of the primary variable will be imputed using the Last observation carried forward (LOCF) approach: if available, post-baseline observations obtained at Visit 2 conducted at day 5 since the start of treatment will be used to impute missing values at Visit 3, day 10.

Supportive analysis will be performed on Valid Case Analysis set using assessed data only.

Descriptive statistics will be presented for pain intensity values and changes from baseline at 10 days after the start of treatment by treatment group and overall.
Descriptive statistics will be presented for FAS (for both values imputed by LOCF and unimputed values) and VCAS.

Mean values of pain intensity at baseline and at day 10 since the start of treatment will be presented on bar chart with whiskers representing 95% CI.

5.5.2 Pain intensity and pain-related disability

Descriptive statistics will be presented for pain intensity values and changes from baseline by visit and by treatment group as well as for the whole population. For Visits 3-5 descriptive statistics will be presented for both values imputed by LOCF and unimputed values.

Changes from baseline in pain intensity measured on 0-10 points NRS scale at 5, 24 and 38 days after will be compared between groups using ANCOVA models similar to those used for the analysis of the primary variable.

A mixed model repeated measures will be used to analyse change from baseline in pain intensity over time. The model will include a random effect for subject and fixed effect terms for treatment, visit, treatment-by-visit interaction, baseline pain intensity. An unstructured covariance structure will be used to model the within-subject errors. If this model fails to converge, other covariance structures will be tested.

Descriptive statistics for pain-related disability score at baseline and at 10 days after the start of treatment as well as for the change from baseline at 10 days after the start of treatment by treatment group and overall will be provided.

Change from baseline in pain-related disability as measured by Roland Morris disability questionnaire at 10 days after the start of treatment will be compared between groups using analysis of covariance (ANCOVA) model with treatment group as fixed factor and baseline value disability score as a covariate.

The dynamics of pain intensity values by study visit (including group mean values and 95% CI of the mean) will be presented graphically using line plot. Mean values of pain-related disability score at baseline and at 10 days after the start of treatment will be presented on bar chart with whiskers representing 95% CI. Additionally, box plot will be presented for pain intensity and pain-related disability score at baseline and at 10 days after the start of treatment with the top and bottom box lines showing the first and third quartiles and the internal bold line representing the median. The whiskers will show the maximum and minimum values, with the exception of outliers (circles) and extremes (asterisks). Outliers are at least 1.5 IQR from the median and extremes are at least 3 IQR from the median.

5.5.3 30% relief in pain intensity

Relief in pain intensity (as measured on 0-10 points NRS) is defined as **100%*(pain intensity at V1- pain intensity at Vk)/ pain intensity at V1**, where Vk is pain intensity at Visits 2 - 5.

The denominator for the proportion will be the number of patients with available pain intensity measurements after imputation using LOCF. Number and proportion of patients showing ≥ 30% relief with respect to pain intensity at 5, 10, 24 and 38 days after the start of

treatment will be presented by treatment group and overall together with 95% confidence intervals for proportion and difference in proportions (Test - Reference) between groups.

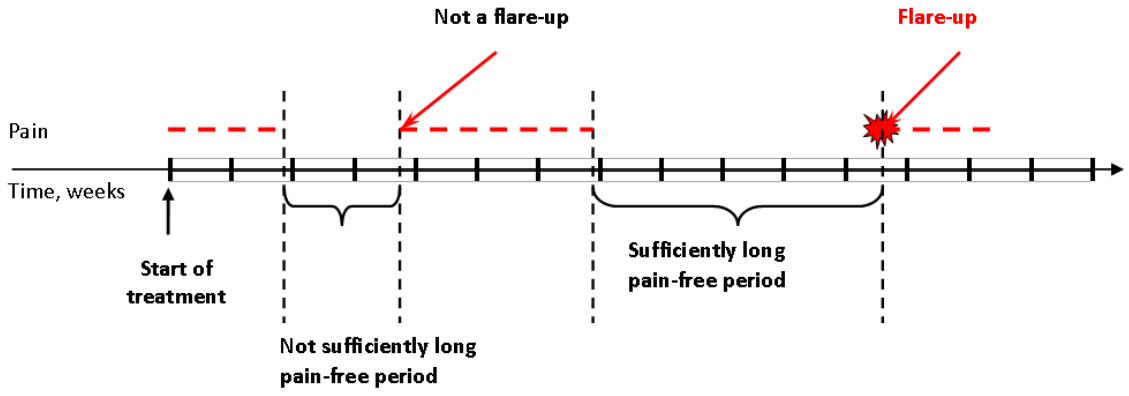
Between-group comparison will be carried out using logistic regression with treatment group as fixed factor and baseline pain intensity as a covariate. Treatment effect will be tested using the corresponding p-value. Odds ratios (Test/Reference) will be presented with 95% confidence intervals.

5.5.4 Pain flare-up

Episode of pain flare-up will be defined as presence of at least 1 day with pain following a period without pain lasting at least 4 weeks (see Figure 1). The occurrence of pain flare-up will be determined by the investigator.

Number and proportion of patients with at least one pain flare-up (as well as with at least one pain flare-up resulting in consultancy with physician, resulting in disruption of daily activity, resulting in NSAIDs) after the start of treatment will be presented by treatment group and overall together with 95% confidence intervals for proportion and difference in proportions (Test - Reference) between groups.
The denominator for the proportion will be the number of FAS patients who had at least one pain-free period with approximately 4 weeks duration registered during the study as noted on the 'Study Termination' page of the CRF.

Percentage of patients with at least one pain flare-up and at least one pain flare-up resulting in consultancy with physician, resulting in disruption of daily activity, resulting in NSAIDs intake among patients who had a sufficiently long pain-free period allowing for such assessment will be compared between groups using Fisher's exact test.



A pain-free period of approximately 4 weeks or longer is considered sufficiently long for the assessment of pain flare-up.

FIGURE 1 PAIN FLARE-UP

5.5.4.1 Number of treatment days with NSAIDs

Number of treatment days with NSAIDs will be calculated using the data collected on the NSAIDs intake during the study.
In order to calculate the total number of treatment days with NSAIDs, first, intersecting or adjacent records will be collapsed, irrespective of the specific drug used; the duration of each of the resulting intake periods will be determined as (End date – Start date + 1) and, finally, all individual duration values will be summed up. In case medication intake is ongoing at the end of study, end date will be imputed by the date of study completion.

Number of days of treatment with NSAIDS will be compared between groups using Wilcoxon–Mann–Whitney test. The data will be presented graphically using box plots. The top and bottom box lines show the first and third quartiles, the internal line represents the median. The whiskers show the maximum and minimum values, with the exception of outliers (circles) and extremes (asterisks). Outliers are at least 1.5 IQR from the median and extremes are at least 3 IQR from the median.

By-patient listings of all the effectiveness derived and raw data will be provided.

5.6 Safety Evaluation

Safety set will be used to assess safety objectives.

5.6.1 Adverse Drug Reactions

ADRs will be presented by the total number (percent) of subjects with ADRs by treatment group and overall, by each system organ class and by each preferred term within a system organ class. To count the number of subjects who experienced each ADR, a subject experiencing the same ADR multiple times will only be counted once for the corresponding preferred term. Similarly if a subject experienced multiple ADRs within the same system organ class, that subject will be counted only once for that system organ class. The denominator for the percentage of subjects reporting ADRs will be the number of subjects in the Safety Population.
For each patient and each adverse drug reaction, the worst severity recorded will be attributed and used in the by-severity summaries.

The following summaries will be provided:

- A summary of the number and percentage of patients reporting an adverse drug reaction by body system, and preferred term
- A summary of the number and percentage of patients reporting an adverse drug reaction related to Milgamma® by body system, and preferred term
- A summary of the number and percentage of patients reporting an adverse drug reaction related to Milgamma compositum® by body system, and preferred term

- A summary of the number and percentage of patients reporting an adverse drug reaction related to celecoxib / etoricoxib / meloxicam / nimesulide by body system, and preferred term
- A summary of the number and percentage of patients reporting an adverse drug reaction by maximum severity, body system and preferred term

A by-patient listing of all adverse drug reactions will be provided. This listing will include: centre, patient identifier, adverse drug reaction (body system, preferred term, reported term), date of onset, date of resolution, severity, relationship to the treatment, seriousness, action taken, outcome.

5.6.2 Deaths, Serious Adverse Drug Reactions, and Other Significant Adverse Drug Reactions

The following summaries of serious adverse drug reactions will be presented:

- A summary of the number and percentage of patients reporting a serious adverse drug reaction by body system, and preferred term
- A summary of the number and percentage of patients reporting an adverse drug reaction leading to discontinuation of the study treatment by body system and preferred term

The following listings are to be provided:

- A by-patient listing of all deaths that occurred during the study
- A by-patient listing of all serious adverse drug reactions
- A by-patient listing of all adverse drug reactions leading to discontinuation of the study treatment.

5.7 Patient Treatment and Patient Satisfaction Evaluation

Patient satisfaction with treatment will be presented descriptively by treatment group as percentage of patients in each category and, additionally, as a continuous variable measured on a Likert-like scale. The comparisons between groups will be performed by means of Wilcoxon–Mann–Whitney test for continuous variable.

Descriptive statistics on the prescribed and actual number of Milgamma® injections, number of days of treatment with Milgamma® compositum will be presented for the group treated with Milgamma®/Milgamma® compositum step-therapy.

The calculation of prescribed number of injections / prescribed number of days of treatment will take into account additional injections prescribed / prolongations of treatment course /

treatment discontinuations due to pain resolution, but will not be reduced in case of treatment discontinuation due to adverse events or other reasons.

The actual number of injections / prescribed number of days of treatment will be calculated by counting the number of injections administered / by summing up all the individual periods of treatment with oral Milgamma® compositum (in days) recorded on the CRF. If the treatment was interrupted, the days patient did not receive the treatment will not contribute to the total number of injections / days of treatment with Milgamma® compositum.

Number and proportion (95% CI) of patients who discontinued the prescribed step-therapy with Milgamma® / Milgamma® compositum will be presented by reason for discontinuation.

The analyses will be performed on the Safety Population.

A by-patient listings of patient treatment and patient satisfaction endpoints will be provided.

5.8 Interim Analysis

No interim analysis will be performed.

5.9 Determination of Sample Size

A between-group difference of 10 points (on a 0–100 scale) for pain is generally considered as the smallest clinically important effect (compared with placebo) [2,6]. However, it is well known that therapy of low back pain with NSAIDs rarely reaches this threshold. The recent meta-analyses [40] estimated the effect of NSAIDs relative to placebo in treatment of acute non-specific low back pain in the immediate (<2 weeks) term as −6.4 points mean difference, 95% CI −10.3 to −2.5, on 100 mm VAS scale. Therefore, 0.5 points difference is chosen to be detected in the current study as half of the 1 point difference conventionally considered as clinically significant in placebo-controlled studies. It is considered attainable in the current study based on results of DOLOR clinical trial [46] which showed 3.8 difference (24,5 ± 18,0 vs. 20,7 ± 18,0) on 100 mm VAS scale between combined treatment with NSAIDs and vitamins B and NSAIDs alone after 3 days of treatment. It is expected that the difference after 10 days of treatment will be at least 0.5 points on 0-10 NRS scale. Such assumptions are also sustained by the results of randomized open-label comparative study of efficacy of Milgamma, diclofenac and their combination for acute lower back pain [4,5] in which the difference between groups was 0.38 after 3 days of treatment and reached 1.17 points after 10 days of treatment.
The sample size of 227 patients per group will provide at least 80% power to detect 0.5 points difference between groups on 0-10 points NRS scale as statistically significant, assuming a standard deviation (SD) of 1.9. The SD for change from baseline at day 10 is conservatively estimated based on the results of the study of efficacy of Milgamma,

diclofenac and their combination for acute lower back pain [4,5] as common standard deviation for pain intensity values at day 10 in the two groups of interest (1.36) multiplied by 2 [7]. This is also in line with the DOLOR study [3] in which the SD of changes from baseline was 18 points on 100 mm VAS scale in both groups.
In order to account for drop-out rate of approximately 10%, it is planned to include 250 patients in each treatment group.

5.10 Changes in the Conduct of the Study or Planned Analysis

None.

6 REPORTING OUTPUT

All outputs will be produced using IBM SPSS version 19 or a later version (if available at ALMEDIS).

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