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

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1 PROTOCOL APPROVAL AND SIGNATURES

Study Protocol has been reviewed and approved by the company Woerwag Pharma LLC.

I confirm that Protocol WP-RU-2018/1«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» is created in accordance with the ethical principles that are consistent with the Declaration of Helsinki, in compliance with Good Pharmacoepidemiology Practices (GPP) and with other applicable legislation on Non-Interventional Studies and Russian regulatory requirements.

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I have read and agree with this study protocol and will follow the described procedures.

I agree to conduct the study according to the protocol in compliance with all applicable laws and regulations.

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6 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
COX	Cyclooxygenase
CRF	Case Report Form
CRO	Contract Research Organization
GPP	Good Pharmacoepidemiology Practices
ICD-10	International Classification of Diseases, 10th revision
IEC	Independent Ethics Committee
INN	International Nonproprietary Names
LOCF	Last Observation Carried Forward
LBP	Low back pain
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSLBP	Non-specific low back pain
RMQ	Roland Morris questionnaire
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
VAS	Visual Analogue Scale
WhoDDE	WHO Drug Dictionary Enhanced

7 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

	Patient treatment and patient satisfaction endpoints: • 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.

8 INTRODUCTION

8.1 BACKGROUND

Low back pain (LBP) is a pain in the lumbar or lumbosacral area. It takes the first place among all non-infectious diseases according to the indicator reflecting the number of years of life lost due to persistent deterioration of health [1-3].

Low back pain is defined as a pain localized between the twelfth pair of ribs and gluteal folds. Acute low back pain includes all episodes of pain with duration up to 4 weeks. If the pain persists from 4 to 12 weeks, it is considered as subacute, and pain lasting 12 weeks and more - as chronic. [1, 4, 53] Relapse is defined for scenario when the pain occurs after at least 6 months of pain-free period. If the pain has resumed after a shorter period, its appearance is considered as an exacerbation of chronic back pain [1, 4, 5].

LBP is one of the most common reasons for visiting the physician, about 6-9% of adults are consulted about this complaint during the year [6]. According to Global Burden of Disease 2010 Study LBP is the leading cause of activity limitation and work absence throughout much of the world, and disability-adjusted life years increased from 58.2 million in 1990 to 83.0 million in 2010 [17]. LBP occurs in the majority (more than 70%) of people during their life, the peak frequency of pain is observed for the age of 35-55 years [10]. According to epidemiological data, 18.3% of the population participated in the survey noted that back pain worries them currently, 30.8% reported that they experienced back pain within the last month, 38.9% – during the last year [11]. According to the survey conducted in Moscow outpatient settings in 2006, 24.9% of 1300 patients turned to the physician because of LBP, while more than half of the respondents (52.9%) were concerned about LBP during previous year [12]. In the UK, about 30% of visits to a general practitioner are related to the pain in back and limbs, and LBP is a reason for visiting a physician in about 7 million cases per year [13].

In most patients, LBP regresses within 1-3 months, however, 60-80% of patients with acute pain periodically experience pain or discomfort during the next year, and among those who experienced disability due to pain, 40% notice repeated episodes of pain with disability [14]. Repeated exacerbations are developed in 24-80% of cases, the peak incidence hits in average age, the frequency of cases remains increased up to 60-65 years, then gradually decreases [11]. Observation of 973 patients with acute LBP showed that almost a third of them (28%) experienced repeated exacerbations during the next year [15]. In general, after an episode of acute LBP, it is continued or reoccurred during the year in one third of patients [1, 4, 5, 16].

Low back pain is associated with enormous social and economic losses due to patients' temporary disability [17-19]. In study published in 2016 pharmacoeconomic analysis revealed that total mean annual cost was found to be $6137.41 for NSAIDs per patient [9]. LBP is one of the most frequent causes of disability, it accounts for 10% of all cases of disability caused by various diseases [19].

In most cases, the cause of acute LBP is a non-life-threatening disease (non-specific low back pain), but it is necessary to exclude serious underlying condition, such as infection, tumor, osteoporosis, ankylosing spondylitis etc. Despite of favorable prognosis of non-specific low back pain inadequate treatment of this disease worsens the prognosis, contributes to its chronicity and significantly reduces the patient's quality of life [1, 4, 20]. The recommendations of experts provide significant input in the management of patients with low back pain. One of the first was the Canadian recommendations proposed 30 years ago and based on the results of 109 randomized trials [21]. Currently, several national and international guidelines for the management of patients with LBP have been developed, based on the

results of a large number of randomized trials (958 by April 2009) to assess the effectiveness of various methods of treatment of low back pain [22-37].

The principles of medical care for patients with LBP vary depending on which specialist conducts the treatment. Patients often refer not only to general practitioners, but also to chiropractors, osteopaths, specialists in acupuncture etc. Some patients come to see neurologists, rheumatologists, orthopedists and neurosurgeons. According to a US study published in 2013, 40% of patients with low back pain refer to physical therapists (chiropractors), 34% to general practitioners, 8% to orthopedists and sports physicians, 3% to neurologists, and 4% to emergency physicians [38]. Common treatment targets of acute non-specific LBP are reduction of pain, improvement of functional ability and prophylaxis of recurrence and chronicity. Important role in the management of patients with acute LBP belongs to non-drug methods. Active lifestyle and, if possible, keeping of routine daily activities is recommended for patients with acute nonspecific back pain. Long-term inactivity and disability worsen the prognosis for such patients. A meta-analysis of several studies has shown that active lifestyle in acute nonspecific back pain improves the course of the disease. [1, 2, 22, 37]. It is also very important to inform the patients about the nature of the disease, its favorable prognosis and necessity to maintain physical activity. The educational programs for patients are considered as a component of patient management program despite the fact that it increases the cost of treatment it increases the cost of treatment [1, 4, 22].

In clinical practice non-steroidal anti-inflammatory drugs (NSAIDs) and myorelaxants are the most common method of pharmacotherapy in acute back pain, [1, 22, 32, 39].Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medicines used to treat inflammation, mild to moderate pain, and fever; they are among the most frequently prescribed drugs in modern medicine. Majority of NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (COX-1 and/or COX-2), thus reducing the biosynthesis of prostaglandins, mediators of pain and inflammation. COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. COX-2 is expressed mostly in inflammation and inhibition of COX-2 produces the desirable effects of NSAIDs [40, 41]. Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase, inhibiting both the COX-1 and COX-2 isoenzymes. When nonselective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen) lower stomach prostaglandin levels, ulcers of the stomach or duodenum internal bleeding can result. Most of modern NSAID (such as celecoxib, etoricoxib, meloxicam and nimesulide) are preferential or selective COX-2 inhibitors that do not cause gastrointestinal side effects characteristic of older NSAIDs. There is also concern about the cardiovascular safety of COX-2 inhibitors, while serious gastrointestinal adverse reactions are more closely linked to nonselective NSAIDs, although all NSAIDs have been associated with cardiovascular and gastrointestinal risks including stomach ulcers, constipation, diarrhea, nausea, liver and kidney lab. abnormalities, arterial hypertension, headaches, dizziness, leg swelling allergic reactions etc [40].

Additionally, for many years vitamin B complex is used for the relief of acute local pain syndromes. B vitamins belong to the hydrosoluble group of vitamins, among their major representatives to manage pain there are vitamins B_1 (thiamine), B_6 (pyridoxine) and B_{12} (cyanocobalamin), which have high metabolic activity in the cells of both the central and peripheral nervous system [42]. Possible analgesic and anti-neuralgic effects of vitamin B complex (especially vitamins B_1 and B_{12}) was shown in experimental animal studies: animal models demonstrated that B-vitamins have antinociceptive and anti-inflammatory properties in the rat tail pressure test, and are able to significantly decrease the responses evoked in spinal dorsal horn nociceptive neurons in the cat [42, 43].

From a clinical standpoint, several studies have reported that thiamine, pyridoxine and cyanocobalamin have an important role for the adequate function of the myelin cover and other cell structures; it is essential for nutrition, axonal transport, neural excitability and neurotransmitter synthesis,

and combined with NSAIDs they present a synergic action in ostheomuscular diseases and pain management [42-44]. The results of clinical research applications of group B vitamins confirm, that vitamins B_1, B_6, B_{12} and containing them complex drugs have pronounced antinociceptive effect [42-46]. For example, the efficacy and safety of parenteral Vitamin B_{12} in alleviating low back pain and related disability and in decreasing the consumption of paracetamol was confirmed in patients with no signs of nutritional deficiency in a double-blind randomised, placebo-controlled study with participation of 60 patients aged between 18 and 65 years with lumbago or sciatic neuritis of mechanical origin [45]. Another clinical randomized, double-blind study included 187 patients that received diclofenac and vitamin B complex (thiamine, pyridoxine and cyanocobalamin twice a day and 185 patients that received diclofenac twice a day. It was demonstrated that combination of diclofenac/vitB complex was superior to diclofenac monotherapy for lower back pain relief after 3 days of treatment [46].

Milgamma® and Milgamma® compositum are vitamin B complexes available in a number of countries worldwide. Milgamma® is a solution for intramuscular injections, which allows to combine in one composition and stabilize vitamins B_1, B_6 and B_{12}, which under normal conditions are mutually destructive. In addition, the composition includes a local anesthetic component, which makes the drug administration less painful and more convenient to use. One 2 ml ampule of Milgamma® contains the active ingredients which are the thiamin hydrochloride (vitamin B_1) 100 mg, pyridoxine hydrochloride (vitamin B_6) 100 mg, cyanocobalamin (vitamin B_{12}) 1 mg and lidocaine hydrochloride 20 mg [47].

Milgamma® compositum is a tablet form of vitamin B complex. When used orally, not all of vitamins B, in particular thiamine (vitamins B_1), have sufficient bioavailability, especially in the presence of concomitant gastrointestinal disorders [50, 53, 54]. This problem can be solved by using fat-soluble forms of medications. Milgamma® compositum contains two active substances: benfotiamin and pyridoxine. Benfotiamine is a lipophilic substance with a thiamine-like activity with a much higher bioavailability than genuine thiamine and it is well absorbed when administered orally [48, 53]. Pyridoxine (vitamins B_6) participates in metabolism of proteins and fats. Both components of medicines potentiate effects of each other. One tablet of Milgamma® compositum contains pyridoxine hydrochloride (vitamin B_6) 100 mg and benfotiamin 100 mg. [48].

The numerous studies performed have shown the positive effect of Milgamma® and Milgamma® compositum on subjective and objective clinical parameters in patients with various nervous system lesions: alcoholic and diabetic polyneuropathy, trigeminal neuralgia, discogenic lumbosacral radiculopathy, etc. [50, 52, 53, 54]. In particular, Milgamma® and Milgamma® compositum have an additional analgesic effect during standard analgesic therapy with various non-steroidal anti-inflammatory drugs. So the open controlled clinical study performed by prof. O. Levin evaluated the short-term and long-term effectiveness of a complex of B vitamins in 38 patients with vertebrogenic lumbosacral radiculopathy suffered from moderate or severe pain during 1 month or longer [49]. One group of patients was treated with diclofenac, and the other group with a combination of diclofenac and vitamin B complex (10 injections followed by oral administration for 2 weeks). A significant and moderate effect after 24 days of treatment with Milgamma® was observed in 66 % of patients, in the control group - in 34 % ($p < 0,05$). After 3 months of therapy pain was absent or minimal in 63% of patients of the main group and in 50% of patients of the control group ($p < 0.05$). Another randomized open comparative study of efficacy of Milgamma®, diclofenac and their combinations for acute pain in the lower back was conducted by prof. A. Danilov: 90 patients with acute back pain were divided into 3 groups: the first group included 40 patients who received 2.0 ml of Milgamma injections for up to 10 days , the second group – 30 patients who took 75 mg diclofenac intramuscularly at per day for up to 10 days, the third group – 20 patients who received daily injections of Milgamma (2.0 ml) and diclofenac (75 mg). [51,52]. The effect of Milgamma® was comparable to diclofenac, which indicates that the combination of vitamin B complex in Milgamma® has an analgesic effect. Combination of diclofenac with Milgamma® was significantly more effective than monotherapy with diclofenac or a complex of

vitamins. More rapid and pronounced reduction of pain was shown in the first days of therapy, thus, the study confirms the effectiveness of the clinical application of Milgamma® in the treatment of acute back pain. Since therapy with NSAIDs in combination with B vitamins is more effective and rapid, Milgamma® and Milgamma® compositum step-therapy could be possibly reduce side effects of NSAIDs.

8.2 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 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 achievement of maximal pain relief with reducing use of NSAIDs that have many side effects.

9 STUDY PURPOSE AND OBJECTIVES

9.1 PURPOSE

The purpose of this observational study is to assess the effectiveness and safety of add-on Milgamma®/ Milgamma® compositum step-therapy in patients with acute non-specific low back pain receiving modern NSAIDs in routine medical practice.

9.2 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.

9.3 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.

- To assess long-term effectiveness of Milgamma®/ Milgamma® compositum step-therapy 3 months after start of treatment in routine medical practice.

10 INVESTIGATIONAL AND ANALYSIS PLAN

10.1 STUDY DESIGN AND PLAN

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. Planned study duration is approximately 10 months (clinical part).

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. Decision concerning prescribing certain treatment should be made by the treating physician prior to proposal to participate in the study and prior to informed consent signing.

After enrollment in the study each patient will be observed over a period of approximately 94 days. 9 visits/phone contacts are planned to be conducted during this period. Information about patient's condition, pain intensity, pain flare-ups, satisfaction with the treatment, patient's disability, therapy used for acute back pain treatment, data on safety will be collected during these visits.

Patients will undergo clinical assessment and receive the standard medical care as usual determined by the treating physician based on clinical judgment and national recommendations. Patients will not receive experimental treatment as a consequence of their participation in the observational study.

10.2 STUDY POPULATION

It is planned to enroll 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.

10.2.1 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.

10.2.2 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.

Investigator(s) should keep the subject screening log of patients who entered screening.

The Investigator(s) will obtain signed informed consent from the patient eligible for the current study before any study specific procedures are performed. The patient will be assigned a unique enrolment number. If the patient withdraws from participation in the study, then his/her enrolment number cannot be reused.

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled.

10.2.3 SITE SELECTION REQUIREMENTS

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).

10.3 STUDY DURATION

Anticipated study duration is from Q4 2018 till Q4 2019. Period of clinical part of the study is planned to be approximately 10 months.

10.4 STUDY CONDUCT

Flow chart of the study is shown in the Table 1.

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.

10.4.1 STUDY PROCEDURES:

All procedures will be conducted in accordance with routine practice. 9 visits are planned to be conducted during the study. First and third visits will be conducted on-site (Visit 1 and Visit 3) and the rest can be performed as either phone calls or on-site visits.

VISIT 1

At Visit 1 the patient will sign informed consent form. After that the investigator can conduct all study-related activities. At the moment of Visit 1 treatment with NSAIDs or with NSAIDs + Milgamma® / Milgamma® compositum should have been prescribed, but not started yet. Following data will be collected at Visit 1:

- Subject Information
- ICF procedure
- Check of inclusion/ exclusion criteria
- Demographics and baseline characteristics (date of birth, sex, height, weight, body mass index).
- Medical History:
    - Description of diagnosis of low back pain
    - Start date of current episode of acute non-specific low back pain.
    - Other existing clinically relevant conditions.
- Prescribed therapy for back pain management:
    - Type of NSAIDs, other medicines (if applicable), doses, duration.
    - For patients prescribed with Milgamma® / Milgamma® compositum number of Milgamma® injections and number of treatment days with oral Milgamma® compositum should be indicated.
    - Further therapies prescribed/ received in the context of low back pain (e.g. cryo therapy, acupuncture, manual therapy etc.)
- Concomitant medication
- Pain intensity using NRS.
- Pain-related disability with Roland Morris disability questionnaire.

VISIT 2

Visit 2 can be conducted as either phone call or on-site visit at day 5 of therapy. Following data will be collected at Visit 2:

- Pain intensity using NRS.
- Presence of day(s) with pain since previous contact.
- Patient's satisfaction with the treatment using 5-point verbal rating scale (1= very dissatisfied, 2= dissatisfied, 3= neutral, 4= satisfied, 5= very satisfied).

- Therapy for back pain management:
    - Current treatment with NSAIDs, other medications (if applicable), doses, duration.
    - For patients prescribed with Milgamma® / Milgamma® compositum - current treatment with these products.
    - Concomitant non-drug treatment for low back pain management
- Adverse drug reactions occurred since start of therapy.

VISIT 3

Visit 3 should be conducted at Day 10 from the start of therapy. Following data will be collected at Visit 3:

- Pain intensity using NRS.
- Presence of day(s) with pain since previous contact.
- Pain-related disability with Roland Morris disability questionnaire.
- Patient's satisfaction with the treatment using 5-point verbal rating scale (1= very dissatisfied, 2= dissatisfied, 3= neutral, 4= satisfied, 5= very satisfied).
- Therapy for back pain management:
    - Current treatment with NSAIDs, other medications (if applicable), doses, duration.
    - For patients prescribed with Milgamma® / Milgamma® compositum - current treatment with these products.
    - Concomitant non-drug treatment for low back pain management
- Adverse drug reactions occurred since previous visit.

VISIT 4

The visit 4 will be conducted as either phone call or on-site visit at day 24 after start of therapy. Following information will be collected:

- Pain intensity using NRS.
- Presence of day(s) with pain since previous contact.
- Patient's satisfaction with the treatment using 5-point verbal rating scale (1= very dissatisfied, 2= dissatisfied, 3= neutral, 4= satisfied, 5= very satisfied).
- Therapy for back pain management:
    - Current treatment with NSAIDs, other medications (if applicable), doses, duration.
    - For patients prescribed with Milgamma® / Milgamma® compositum - current treatment with these products.
    - Concomitant non-drug treatment for low back pain management
- Adverse drug reactions occurred since previous visit.

VISIT 5

Visit 5 should be conducted at day 38 after start of therapy as either phone call or on-site visit. It is anticipated that step-therapy with Milgamma®/ Milgamma® compositum will be completed by this time. Following data will be collected at Visit 5:

- Pain intensity using NRS.
- Presence of days with pain since previous contact.
- Presence of new pain flare-up.
    - In case of presence of pain flare-up, assessment of:
        - Whether pain flair-up resulted in consultancy with physician or professional management.
        - Whether pain flair-up resulted in disruption of daily activity.
        - Whether pain flair-up resulted in NSAIDs intake.
- Patient's satisfaction with the treatment using 5-point verbal rating scale (1= very dissatisfied, 2= dissatisfied, 3= neutral, 4= satisfied, 5= very satisfied).
- Therapy for back pain management:
    - Current treatment with NSAIDs, other medications (if applicable), doses, duration.
    - For patients prescribed with Milgamma® / Milgamma® compositum - current treatment with these products.
    - Concomitant non-drug treatment for low back pain management
- Adverse drug reactions occurred since previous visit.

VISITS 6, 7, 8

These visits will be conducted at day 52, 66 and 80 after start of therapy as either phone calls or on-site visits. Following information will be collected on these visits:

- Pain intensity using NRS.
- Presence of days with pain since previous contact.
- Presence of new pain flare-up.
    - In case of presence of pain flare-up, assessment of:
        - Whether pain flair-up resulted in consultancy with physician or professional management.
        - Whether pain flair-up resulted in disruption of daily activity.
        - Whether pain flair-up resulted in NSAIDs intake.
- Therapy for back pain management:
    - Current treatment with NSAIDs, other medications (if applicable), doses, duration.
    - For patients prescribed with Milgamma® / Milgamma® compositum - current treatment with these products.

- Concomitant non-drug treatment for low back pain management

- Adverse drug reactions occurred since previous visit.

VISIT 9/ EARLY DISCONTINUATION VISIT

Visit 9/ early discontinuation can be conducted as either phone call or on-site visit after 3 months (day 94) from start of therapy or in case of patient's early discontinuation from the study. Following data will be collected:

- Pain intensity using NRS.
- Presence of days with pain since previous contact.
- Presence of at least 1 pain-free period with approximately 4 weeks duration during the study.
- Presence of new pain flare-up.
  - In case of presence of pain flare-up, assessment of:
    - Whether pain flair-up resulted in consultancy with physician or professional management.
    - Whether pain flair-up resulted in disruption of daily activity.
    - Whether pain flair-up resulted in NSAIDs intake.
- Patient's satisfaction with the treatment using 5-point verbal rating scale (1= very dissatisfied, 2= dissatisfied, 3= neutral, 4= satisfied, 5= very satisfied).
- Therapy for back pain management (if it is continued):
  - Current treatment with NSAIDs, other medicines (if applicable), doses, duration.
  - For patients prescribed with Milgamma® / Milgamma® compositum - current treatment with these products.
  - Concomitant non-drug treatment for low back pain management
- Adverse drug reactions occurred since previous visit.
- Study completion status and reason for early discontinuation, if applicable (patient lost to follow-up, patient withdrew consent, administrative reasons, pain resolution, adverse event, death, other).

10.4.2 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:

1) Modern NSAIDs (preferential/selective COX-2 inhibitors);

2) 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.

10.5 STUDY ASSESSMENTS

10.5.1 EFFECTIVENESS

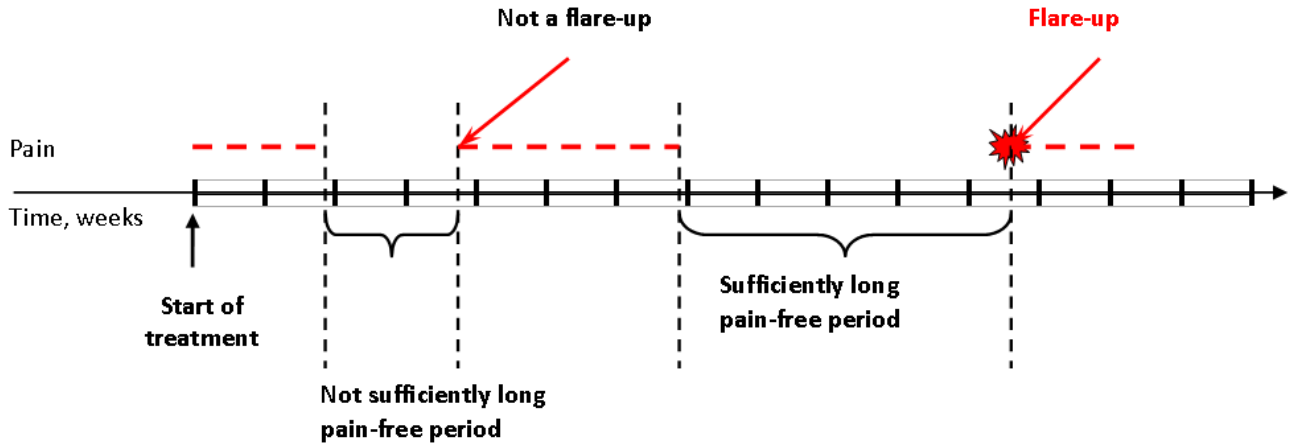
Effectiveness assessments will be performed at visits 1-9 based on patient-reported outcome instrument for pain intensity, as measured on 0-10 point NRS (numeric rating scale).

Numeric Rating scale is 11-step scale for assessment of pain intensity at the moment of patient's examination, where 0=No pain and 10= Worst pain imaginable. The scale will be used in verbal communication, via the phone as well. The Investigator should ask the patient to assess pain intensity at the moment of examination by rating from 0 to 10, where 0 is "No pain" and 10 is "Worst pain imaginable". The answer of patient should be fixed at source documents and in CRF [57].

Patients' disability will be assessed at visits 1 and 3 on the basis of patient-reported outcome instrument Roland Morris disability questionnaire. This instrument has been translated into Russian and validated [55] (Appendix 1). Roland Morris questionnaire (RMQ) is a commonly used patient-reported outcome measure that assesses pain-related functional status; its measurement properties are consistent with or better than those of competing measures. The RMQ is a 24-item self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale. Items are scored 0 if left blank or 1 if endorsed, for a total RMQ score ranging from 0 to 24; higher scores represent higher levels of pain-related disability. The RMQ has been shown to yield reliable measurements, which are valid for inferring the level of disability, and to be sensitive to change over time for groups of patients with low back pain. The patient is instructed to put a mark next to each appropriate statement. Add up the total number of marked statements to get a patient's score. [57, 58]

Assessment of long-term efficacy will be conducted based on collection of episodes of pain flare-ups. 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. Description of pain flare-up is adapted from widely used definition of recurrence of pain episode according to which it should be preceded by at least 1 month of pain-free period [64,65,66]. Presence of pain flare-up will be determined by the investigator during conversation with the patient. Assessment of pain flare-ups will be started from visit 5 (day 38 of treatment) and will be conducted regularly in accordance with visit schedule. To judge whether pain flare-up occurred the investigator should 1) consider data on patient's assessment of pain intensity with NRS at current and previous visits, as well as information regarding presence of days with pain between visits, 2) determine as precisely as possible when was the last time the patient experienced pain and when the pain returned to decide whether the pain-free period was long enough to consider that a flare-up occurred. For collection of data on presence of day(s) with pain since previous contact, the investigator will ask the patient whether there was at least 1 day since previous contact when patient experienced pain (see Figure 1 below).

If a flare-up is identified the investigator will ask whether patient had consultancy with physician, at least 1 day unable to carry out usual daily activities (including work absence), or received NSAIDs (at least 1 dose) because of low back pain since previous contact.



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

Number of treatment days with NSAIDs will be evaluated based on information on NSAIDs intake by the patient during the whole observational period.

10.5.2 PATIENT TREATMENT AND SATISFACTION

Prescribed and actual number of Milgamma® injections and prescribed and actual number of treatment days with oral Milgamma® compositum will be assessed. Data on treatment with NSAIDs will be collected including trade name, formulation, dose, route of administration and duration.

Patient satisfaction with the treatment will be estimated at Visits 2, 3, 5 and 9 using 5-point verbal rating scale (1= very dissatisfied, 2= dissatisfied, 3= neutral, 4= satisfied, 5= very satisfied).

10.5.3 SAFETY

Safety assessment will be based on frequency and severity of ADRs recorded during the study.

10.5.4 EVALUATION CRITERIA (ENDPOINTS)

All effectiveness endpoints will be compared between treatment groups.

10.5.4.1 PRIMARY ENDPOINT:

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

10.5.4.2 SECONDARY ENDPOINTS:

EFFECTIVENESS ENDPOINTS

- 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 ENDPOINTS:

- 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.

11 QUALITY MANAGEMENT AND MONITORING PROCEDURES

The sponsor should ensure that the study is conducted in accordance with the protocol and all applicable regulations (mentioned in relevant sections below).

11.1 QUALITY CONTROL

11.1.1 MONITORING

Frequency of monitoring visits, responsibilities and methods for monitoring will be described in detail a Monitoring Plan, which has to be finalized previously to study start.

Before the study initiation, the assigned monitor will establish the adequacy of the facilities and the investigator's capability to select the patients appropriately.

"Green light" for study sites initiation will be given at the time point when all activities prior to study execution are complete and documented (including approval of Monitoring Plan, signing the contracts with sites and investigators, preparation of Trial Specific Trial Master File and Investigator File, accomplishment of all start-up project-related tasks).

At the initiation visit, monitor will discuss with the investigators study protocol and CRF, as well their responsibilities with regards to protocol compliance. During the study clinical sites will be visited by the monitor on a sample basis to check the progress of enrolment, completeness and correctness of ICFs, the completeness of patient' source documents, the accuracy of entries in the CRFs and the adherence to the protocol and all applicable regulatory requirements. Investigators and other study personnel must be available to assist a monitor during these visits.

The investigator must maintain source documents, including all demographic and medical information, as well as the results of all assessments for each patient in the study. The investigator also has to keep signed copy of informed consent for each patient.

The investigator agrees for conduction of regular visits to the site by authorized employees of the CRO and the Sponsor. The investigator must have sufficient time for the visit. The investigator must give a monitor, auditors, authorized employees from Woerwag Pharma, IECs and regulatory authorities (if required) access to all relevant source documents to confirm their consistency with the CRF data. Checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

11.1.2 DATA QUALITY CONTROL

Collected data from the CRFs will be entered into specially designed study database using double data entry method and undergo electronic verification. The Data Management staff will check entered data for completeness and accuracy. The authorized Data Management personnel will enter detected errors or omissions on Data Query Forms, which will be returned to the participating physician for resolution. The signed and dated resolved Data Query Forms are sent to the company authorized by Woerwag Pharma for data correction and the copies kept by the participating physician.

Detailed information on data management procedures and data quality check will be described in Data Management Plan.

11.2 QUALITY ASSURANCE

11.2.1 AUDITS

Audits can be conducted during the study, as well as after its completion. Audits can be conducted in the clinical site or CRO. The investigator must give to auditors access to the Study-related documents and information. The Sponsor and any persons authorized to act on the Sponsor's behalf for the purpose of audit will be given unhindered access to CRO premises and its Study-related documents and information.

Such documents and information shall include (without limitation) relevant materials and data, related to the Study, and documents describing personnel's professional training and experience.

11.2.2 TRAINING FOR STUDY STAFF

Training for investigators on study procedures will be conducted during Investigators meeting, on Site Initiation Visits and during the study if necessary.

12 DATA COLLECTION AND MANAGEMENT

Each enrolled patient will be assigned with unique identification number (the last available from the pre-designed sequence). The individual Case Report Form (CRF), specially designed for this study, will be completed for each patient enrolled.

The collection of data from out-patient medical records, as well as collection of data received by a physician during the routine patient examination will be performed. Any special data collection procedures are not stipulated within the framework of this study. All information received during the study period should be documented in out-patient medical records. The information necessary for CRF should be entered based on the patient source documents. Source documents are kept by physician.

Data collection, data entry and management will be performed by the company authorized by Woerwag Pharma.

The originals of completed CRFs will be sent on a regular basis, after approval by the monitor by the participating physicians to the company authorized by Woerwag Pharma. Copies of CRFs, as well as the original signed Informed Consents forms will be kept by the physician during the study and after the study completion during 5 years.

Relevant drug therapy and concomitant therapy entered into the database will be coded based on WhoDDE current version. Medical history/current medical conditions and adverse dug reactions, as well as non-pharmacological therapy will be coded using current version of the Medical Dictionary for Regulatory Activities (MedDRA). Database will have to be completed, and then passed appropriate quality check, considered to be full and accurate, and then will be locked. Any changes after the database lock will be possible only with written permission of sponsor, project manager, statistician and data manager. Collected data will be analyzed.

Essential study documents must be retained by the participating physician for 5 years. No source documents, containing patients' personal data, should be taken away from the physician.

Data Management processes will be defined in Data Management Plan.

13 DATA ANALYSIS PLANS

A Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a more technical and detailed description of the planned statistical analyses.

All comparisons will be conducted at the two-sided level of significance 5%. Between-group comparisons of change from baseline in pain and disability will be performed using analysis of covariance in order to estimate treatment effect adjusted for baseline pain/disability. Inclusion of center effect into the model will also be considered.

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).

Baseline data as well as all data obtained during the observation period will be presented descriptively by group as follows: the number of observations, mean and standard deviation, median, first and third quartiles, minimum and maximum, lower 95% CI of mean and upper 95% CI of mean will be calculated for continuous variables, and the absolute frequencies and percentage of patients presenting the given feature will be calculated for qualitative variables. Baseline characteristics among groups will be compared using the Fisher's exact test for binary variables and the Wilcoxon–Mann–Whitney test for continuous variables.

The results on the study endpoints (by treatment group as well as difference between groups) will also be presented with two-sided 95% confidence intervals, where applicable. The results on effectiveness variables will be presented graphically.

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.

Similar approach will be used for the primary analysis of change from baseline in pain intensity at day 38 since the start of treatment. Supportive analysis will be conducted using complete case approach.

13.1 Definitions of Analysis Datasets

All Enrolled Set as all patients who signed informed consent for entry into the study.

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.

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 efficacy variable is available. VCAS will be used for sensitivity analysis of the primary endpoint.

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.

13.2 Effectiveness Analyses

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. Similar ANCOVA models will be fitted for change from baseline in pain intensity at each individual time point (secondary endpoints). Mean change from baseline along with 95% confidence interval estimated using the appropriate model will be presented by treatment group.

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 on disability scale as a covariate.

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.

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. Treatment effect will be tested using the corresponding p-value and odds ratios will be presented with 95% confidence intervals.

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.

Number of days of treatment with NSAIDS will be compared between groups using Wilcoxon–Mann–Whitney test.

13.3 SAFETY

Safety assessment will be based on the analysis of adverse drug reactions (ADRs) frequency and severity. Adverse drug reactions will be coded with the current version of Medical Dictionary for Regulatory Activities. ADRs will be presented by the total number (percent) of patients with ADRs by treatment group, by each system organ class and by each preferred term within a system organ class. ADRs will also be presented by maximum severity grade. Safety analyses will be performed on the Safety Population.

13.4 JUSTIFICATION OF SAMPLE SIZE

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 (H0):

H0: μ2 – μ1 ≥ 0

Alternative hypothesis (HA):

HA: μ2 – μ1 < 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.

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) [40,56]. 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 ($24{,}5 \pm 18{,}0$ vs. $20{,}7 \pm 18{,}0$) 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

[51,52] 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 [51,52] as common standard deviation for pain intensity values at day 10 in the two groups of interest (1.36) multiplied by $\sqrt{2}$ [63]. This is also in line with the DOLOR study [46] 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.

13.5 Other Analyses

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.

Data on prescribed and actual number of Milgamma® injections and number of treatment days with oral Milgamma® compositum will be summarized descriptively.

13.6 Study limitations

Like any other non-interventional study, this study has some limitations. One of the most important limitations is the lack of randomization which might lead to selection bias. The comparability between groups at baseline with respect to the most important demographic and anamnestic characteristics will be assessed and will be discussed in the final report. The second limitation is related to variety of back pain management approaches by different physicians due to lack of national clinical guidelines on this condition. Another limitation is that in routine practice therapy with Milgamma® / Milgamma® compositum is usually prescribed to patients with a more pronounced neuropathic component of pain syndrome compared to patients prescribed NSAIDs monotherapy. Next limitation is different duration of therapy for each patient. All assessments will be done at fixed time points from the start of therapy and will be interpreted accordingly. To reduce the risk of patients' drop-out during the study, all visits except Visits 1 and 3 can be conducted as phone calls.

14 Collection and Reporting of Adverse Events/Adverse Drug Reactions and Quality Complaints

To allow continuous monitoring of product safety, all ADRs and other safety information as defined below have to be documented by the investigator and reported to the sponsor.

14.1 Definition of Adverse Drug Reaction and Other Safety Information

14.1.1 Definition of Adverse Events (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. 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.

14.1.2 Adverse Drug Reaction (ADR)

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.

14.1.3 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

An AE or ADR that fulfils at least one of the following criteria:

- Results in death
- Is life-threatening (this implies that the patient was at risk of death at the time of the event; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing in-patient hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above (e.g. suspected transmission via a medicinal product of an infectious agent, thromboembolic events, or other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria, e.g., 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). Medical and scientific judgement should be exercised in deciding whether other situations should be considered.

14.1.4 Other Relevant Drug Safety Information

Any safety information relating to:

- Pregnancies/breastfeeding.
- Drug abuse (persistent, sporadic or intentional excessive use of a medicinal product inconsistent with the SmPC or acceptable medical practice which is accompanied by harmful physical or psychological effects).

- Misuse (situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information)
- Overdose (administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied)
- Medication errors (an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient).
- Interactions with other medicinal products or devices.
- Occupational exposure (an exposure to a medicinal product as a result of one's professional or non-professional occupation).
- Off-label use (situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information).
- Lack of effectiveness.

that is associated with Milgamma® or Milgamma® compositum, even if no ADRs occurred.

14.2 Collection of Adverse Drug Reactions during the Study

Every patient must be examined by the investigator regarding appearance of adverse drug reactions, which should be classified in accordance with their connection with the medicinal product(s) used for LBP treatment. During the Study ADRs (both non-serious and serious) are actively collected if an Investigator suspects that they can be causally related to the medicinal product used for LBP treatment under study. For each ADR the following variables will be collected;

- Description of ADR
- ADR start date and end date (if applicable)
- ADR severity (mild, moderate, severe) (see details in Appendix 3)
- ADR seriousness (whether an ADR is serious or not)
- Medicinal product which is suspected to have casual relationship with an ADR, including start and stop dates of medicinal product administration.
- Action taken with regard to a suspected medicinal product
- Outcome of ADR

All ADRs will be recorded by the Investigator in CRF. Each month safety information collected in database will be provided to the Sponsor by Data Manager of CRO ALMEDIS.

14.3 Reporting of ADRs, Other Safety Information and Quality Complaints

All suspected ADRs, other safety information and quality complaints associated with the administration of Milgamma® or Milgamma® compositum (or any other Woerwag Pharma product, if applicable) have to be reported to Woerwag Pharma LLC:

Contacts:
Anna Shagako, Clinical Trials Manager / Authorized Person of Pharmacovigilance
Phone: +7 495 269 69 20 ext. 116
Cell: +7 985 233 32 46

Denis Zhivotov, Head of Regulatory Department / Deputy Authorized Person of Pharmacovigilance
Phone: +7 495 269 69 20 ext. 117
Cell: +7 985 179 20 04

E-mail: adr@woerwagpharma.ru

SADRs including safety information as in Section 13.1.4 associated with **SADR have to be reported by an Investigator using special form provided by the Sponsor immediately by email (adr@woerwagpharma.ru, within 24 hours).** Non-serious ADRs and other safety information should be reported to the sponsor via completion of corresponding CRF form, which will be periodically collected by a CRO or Woerwag Pharma representatives. Each month safety information collected in database will be provided to the Sponsor by Data Manager of CRO ALMEDIS.

Patients should be asked to immediately inform an Investigator of any AEs or other relevant safety information. An Investigator has to report ADRs and other relevant drug safety information to the sponsor.

For more information about possible ADRs and other safety information, please refer to the local SmPC (see Appendix 2 to the Study Protocol).

Safety events which are suspected to be related to other medicinal products used for LBP treatment should be reported by the investigator to the responsible marketing authorization holder in frames of spontaneous reporting as required by Guidelines for Good Pharmacovigilance Practices of Eurasian Economic Commission and order of the Federal Service for pharmacovigilance dated February 15, 2017 No. 1071 [61, 62].

The local Woerwag Pharma pharmacovigilance team is responsible to inform the Global Woerwag Pharma Pharmacovigilance Department (dso@woerwagpharma.com) within the below defined timelines: SADRs including safety information as in 13.1.4 associated with SADR as soon as possible, but no later than 5 (five) calendar days. If there is a potential fatal or life threatening ADR Global Woerwag Pharma Pharmacovigilance Department must be informed within 24 hours.

The local Woerwag Pharma pharmacovigilance team is also responsible to inform the Russian Health Authorities on SADRs in accordance with Guidelines for Good Pharmacovigilance Practices of Eurasian Economic Commission and order of the Federal Service for pharmacovigilance dated February 15, 2017 No. 1071 [61, 62]:

- Within 15 calendar days - for SADRs including cases of transmission of infectious disease, cases of drug abuse, cases of deliberate overdose,
- Within 3 days - for fatal and life-threatening SADRs.

15 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

15.1 REGULATORY AND ETHICAL COMPLIANCE

This study is a non-interventional study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a study protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data [59]. This observational study was designed and will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, in compliance with Good Pharmacoepidemiology Practices (GPP) and with other applicable legislation on Non-Interventional Studies. The study also will be carried out in keeping with applicable Russian regulatory requirements [60, 61, 62].

Before implementing this study, the main documents of the study (including Protocol and Subject Informed Consent Form) must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC). The Ethics Committee must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

15.2 RESPONSIBILITIES OF THE INVESTIGATOR AND IEC

The Investigator will perform the observational study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the observational study and in accordance with currently acceptable techniques and know-how.

The planned ethical review of the study will be aimed, primarily, to ethical assessment of the possibility of patient data using for CRF completion and possibility of third party access to the source documentation of patients. The investigator must keep all information provided by the company-sponsor in strict confidence and request similar confidentiality from his/her staff and the Independent Ethics Committee. Study documents provided by the company-sponsor or its representative will be safeguarded appropriately to ensure their confidentiality. The information provided by the company-sponsor to the investigator may not be disclosed to others parties without direct written authorization from the company-sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study.

15.3 INFORMED CONSENT

The Investigator at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of this observational study. Patients must also be notified that they are free to discontinue from the study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided.

The Patient Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the study.

The Patient Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The signed and dated patient informed consent must be obtained before any specific procedure for the study is performed.

The Investigator must store the original, signed patient informed consent form for 5 years. A copy of the signed patient informed consent form must be given to the patient.

15.4 Publications and Other Rights

The sponsor has sole ownership of all data, results, reports, and any other information collected and full rights of publication based on data from this study and will maintain full access to the database.

Upon the study completion and finalization of the clinical study report the results of this study will be submitted for publications. Publications will be based on data from all centers, analyzed as stipulated in the protocol. The investigator agrees not to publish or publicly present any interim results of the study or data gathered from one center or a small group of centers before the global publication without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication that report any results of the study. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts with regard to the following concerns:

- Proprietary information that is protected by the provisions contained in;
- The accuracy of the information contained in the publication;
- To ensure that the presentation is fairly balanced and in compliance with applicable regulations;
- Others.

15.5 Study Documents and Records Retention

The investigator must complete the CRF as required by the protocol. All information on CRF must be traceable to the source documents in the patient's medical file. Data on patients collected on CRF during the study will be anonymous to ensure patient confidentiality. Patients will be identified in the CRF and the database only by the patient's number. No source documents, containing patients' personal data, should be taken away from the clinical site. All study documents shall be made available if required by the company-sponsor or its designee, auditors or relevant health authorities.

During the study and after the study termination the investigator must maintain copies of all documents and records relating to the conduct of the study. Essential study documents must be retained by the investigator during 5 years.

16 Investigators and Study Administrative Structure

16.1 Sponsor

The sponsor of this study is the company «Woerwag Pharma LLC».

16.2 Investigators

Investigators should have qualification and experience for management of patients with acute non-specific low back pain. The sponsor will contact and select all investigators, who, in turn, will select their staff.

16.3 OTHER PARTICIPANTS

CRO ALMEDIS will be responsible for essential documents preparation, study conduction and management, data management, biostatistics and study report writing.

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APPENDIX 1

The Roland-Morris Disability Questionnaire

When your back hurts, you may find it difficult to do some of the things you normally do.

This list contains sentences that people have used to describe themselves when they have back pain. When you read them, you may find that some stand out because they describe you today.

As you read the list, think of yourself today. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one. Remember, only tick the sentence if you are sure it describes you today.

1. I stay at home most of the time because of my back.
2. I change position frequently to try and get my back comfortable.
3. I walk more slowly than usual because of my back.
4. Because of my back I am not doing any of the jobs that I usually do around the house.
5. Because of my back, I use a handrail to get upstairs.
6. Because of my back, I lie down to rest more often.
7. Because of my back, I have to hold on to something to get out of an easy chair.
8. Because of my back, I try to get other people to do things for me.
9. I get dressed more slowly then usual because of my back.
10. I only stand for short periods of time because of my back.
11. Because of my back, I try not to bend or kneel down.
12. I find it difficult to get out of a chair because of my back.
13. My back is painful almost all the time.
14. I find it difficult to turn over in bed because of my back.
15. My appetite is not very good because of my back pain.
16. I have trouble putting on my socks (or stockings) because of the pain in my back.
17. I only walk short distances because of my back.
18. I sleep less well because of my back.
19. Because of my back pain, I get dressed with help from someone else.
20. I sit down for most of the day because of my back.
21. I avoid heavy jobs around the house because of my back.
22. Because of my back pain, I am more irritable and bad tempered with people than usual.
23. Because of my back, I go upstairs more slowly than usual.
24. I stay in bed most of the time because of my back.

Note to users:

This questionnaire is taken from: Roland MO, Morris RW. A study of the natural history of back pain. Part 1: Development of a reliable and sensitive measure of disability in low back pain. Spine 1983; 8: 141-144

The score of the RDQ is the total number of items checked – i.e. from a minimum of 0 to a maximum of 24.

It is acceptable to add boxes to indicate where patients should tick each item.

The questionnaire may be adapted for use on-line or by telephone.

APPENDIX 2

Local Summary of Product Characteristics for Milgamma® and Milgamma® compositum will be attached as separate documents.

APPENDIX 3

Following definitions should be used for assessment of ADR severity:

Mild	An experience that is usually transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. Includes as well transient laboratory test alterations
Moderate	An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes as well laboratory test alterations indicating injury, but without long-term risk.
Severe	An experience that requires therapeutic intervention. The experience interrupts usual daily activities.