



Title: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Trial to Study the Efficacy and Safety of Cyclobenzaprine HCl Extended Release (CER) 15 mg in Subjects with acute cervical and/or lower back pain due to Muscle Spasms of Local Origin

NCT Number: NCT02814565

Protocol Approve Date: 16 Aug 2016

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- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.



PROTOCOL

Title

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Trial to Study the Efficacy and Safety of Cyclobenzaprine HCl Extended Release (CER) 15 mg in Subjects with acute cervical and/or lower back pain due to Muscle Spasms of Local Origin

Short title

Cyclobenzaprine HCl Extended Release 15mg versus Placebo in Treatment of acute cervical and/or lower back pain due to Muscle Spasms of Local Origin

Sponsor: Takeda Pharmaceutical LLC.,
2, bld.1, Usacheva ul.
Moscow 119048, Russia

Study Number: CYC-RR-001

IND Number: N/A

EudraCT Number: N/A

Date: 16 Aug 2016 **Amendment Number:** 3

Compound: Cyclobenzaprine
HCl Extended
Release
(Myorix[®])

Amendment History:

Date	Amendment Number	Amendment Type	Region
06 October 2014	Initial Protocol	Not applicable	Russia
01 July 2015	1	Substantial	Russia
19 July 2016	2	Substantial	Russia
16 Aug 2016	3	Non-Substantial	Russia

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Russia Contact
Serious adverse event and pregnancy reporting	Personal Protected Data
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Personal Protected Data	Date	Personal Protected Data	Date
			

Personal Protected Data	Date
	

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Russia

Location of Facility (Country)

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TABLE OF CONTENTS

1.0	ADMINISTRATIVE INFORMATION	2
1.1	Contacts.....	2
1.2	Approval.....	3
2.0	STUDY SUMMARY.....	9
3.0	STUDY REFERENCE INFORMATION	12
3.1	Study-Related Responsibilities	12
3.2	Coordinating Investigator	12
3.3	List of Abbreviations	13
3.4	Corporate Identification	14
4.0	INTRODUCTION	15
4.1	Background	15
4.2	Rationale for the Proposed Study.....	15
5.0	STUDY OBJECTIVES AND ENDPOINTS	17
5.1	Objectives.....	17
5.1.1	Primary Objective	17
5.1.2	Secondary Objective	17
5.1.3	Additional Objectives	17
5.2	Endpoints	17
5.2.1	Primary Endpoints.....	17
5.2.2	Secondary Endpoints.....	17
5.2.3	Additional Endpoints	17
6.0	STUDY DESIGN AND DESCRIPTION	19
6.1	Study Design	19
6.2	Justification for Study Design, Dose, and Endpoints.....	20
6.3	Premature Termination or Suspension of Study or Investigational Site.....	21
6.3.1	Criteria for Premature Termination or Suspension of the Study	21
6.3.2	Criteria for Premature Termination or Suspension of Investigational Sites	21
6.3.3	Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s).....	21
7.0	SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS	22
7.1	Inclusion Criteria.....	22
7.2	Exclusion Criteria	22
7.3	Excluded Medications and Treatments	24
7.4	Diet, Fluid, Activity Control and Treatment Facilities	25
7.5	Criteria for Discontinuation or Withdrawal of a Subject.....	26
7.6	Procedures for Discontinuation or Withdrawal of a Subject	27
8.0	CLINICAL TRIAL MATERIAL MANAGEMENT.....	28

CONFIDENTIAL

8.1	Study Medication and Materials	28
8.1.1	Dosage Form, Manufacturing, Packaging, and Labeling.....	28
8.1.2	Storage	29
8.1.3	Dose and Regimen	29
8.1.4	Overdose	29
8.2	Investigational drug Assignment and Dispensing Procedures	31
8.3	Randomization Code Creation and Storage	31
8.4	Investigational Drug Blind Maintenance	31
8.5	Unblinding Procedure	31
8.6	Accountability and Destruction of Sponsor-Supplied Drugs.....	31
9.0	STUDY PLAN.....	33
9.1	Study Procedures.....	33
9.1.1	Informed Consent Procedure	33
9.1.2	Demographics, Medical History, and Medication History Procedure.....	33
9.1.3	Physical Examination Procedure	33
9.1.4	Weight, Height.....	33
9.1.5	Vital Sign Procedure	33
9.1.6	Primary Efficacy Measurement	33
9.1.7	Documentation of Concomitant Medications	37
9.1.8	Documentation of Concurrent Medical Conditions.....	37
9.1.9	Procedures for Clinical Laboratory Samples	37
9.1.10	Contraception and Pregnancy Avoidance Procedure.....	38
9.1.11	Pregnancy.....	39
9.1.12	ECG Procedure	40
9.1.13	Documentation of Screen Failure	40
9.1.14	Documentation of Randomization	40
9.2	Monitoring Subject Treatment Compliance.....	40
9.3	Schedule of Observations and Procedures.....	41
9.3.1	Screening.....	41
9.3.2	Randomization	41
9.3.3	Visit 2 (Day 3) and Visit 3 (Day 7).....	43
9.3.4	Visit 4 (Day 15) or Early Termination.....	43
9.3.5	Follow-up call	43
9.3.6	Post Study Care.....	44
10.0	PRETREATMENT EVENTS AND ADVERSE EVENTS	45
10.1	Definitions.....	45
10.1.1	PTEs.....	45
10.1.2	AEs.....	45

10.1.3	Additional Points to Consider for PTEs and AEs	45
10.1.4	SAEs.....	47
10.1.5	Severity of PTEs and AEs.....	48
10.1.6	Causality of AEs	48
10.1.7	Relationship to Study Procedures	48
10.1.8	Start Date.....	48
10.1.9	Stop Date.....	48
10.1.10	Frequency.....	49
10.1.11	Action Concerning Study Medication.....	49
10.1.12	Outcome.....	49
10.2	Procedures.....	49
10.2.1	Collection and Reporting of AEs.....	49
10.2.2	Collection and Reporting of SAEs.....	50
10.2.3	Reporting of Abnormal Liver Function Tests.....	51
10.3	Follow-up of SAEs.....	51
10.3.1	Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities.....	51
11.0	STUDY-SPECIFIC COMMITTEES	52
12.0	DATA HANDLING AND RECORDKEEPING	53
12.1	CRFs.....	53
12.2	Record Retention.....	53
13.0	STATISTICAL METHODS	55
13.1	Statistical and Analytical Plans.....	55
13.1.1	Analysis Sets	55
13.1.2	Analysis of Demographics and Other Baseline Characteristics.....	55
13.1.3	Efficacy Analysis	55
13.1.4	Safety Analysis	57
13.2	Interim Analysis and Criteria for Early Termination.....	58
13.3	Determination of Sample Size	58
14.0	CONTROL AND QUALITY ASSURANCE.....	59
14.1	Study-Site Monitoring Visits	59
14.2	Protocol Deviations.....	59
14.3	Quality Assurance Audits and Regulatory Agency Inspections	59
15.0	ETHICAL ASPECTS OF THE STUDY	60
15.1	IRB and/or IEC Approval	60
15.2	Subject Information, Informed Consent, and Subject Authorization.....	60
15.3	Subject Confidentiality	61
15.4	Publication, Disclosure, and Clinical Trial Registration Policy	62
15.4.1	Publication and Disclosure.....	62

15.4.2 Clinical Trial Registration.....	62
15.4.3 Clinical Trial Results Disclosure	63
15.5 Insurance and Compensation for Injury.....	63
16.0 REFERENCES.....	64
Appendix E Instruction for Medical Use – Myorix	73

LIST OF IN-TEXT TABLES

Table 8.a Dose and Regimen	29
Table 9.a Clinical Laboratory Tests.....	38
Table 10.a Takeda Medically Significant AE List.....	47

LIST OF IN-TEXT FIGURES

Figure 6.a Schematic of Study Design	20
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LIST OF APPENDICES

Appendix A Schedule of Study Procedures.....	67
Appendix B Responsibilities of the Investigator.....	69
Appendix C Elements of the Subject Informed Consent.....	70
Appendix D Investigator Consent to Use of Personal Information.....	72
Appendix E Instruction for Medical Use - Myorix.....	72

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical LLC.		Compound: Cyclobenzaprine HCl Extended Release	
Title of Protocol: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Trial to Study the Efficacy and Safety of Cyclobenzaprine HCl Extended Release (CER) 15 mg in Subjects with acute cervical and/or lower back pain due to Muscle Spasms of Local Origin		IND No.: N/A	EudraCT No.: N/A
Study Number: CYC-RR-001		Phase: IIIb	
Study Design: This is a randomized, double-blind, placebo-controlled, parallel-group 2-arm study assessing the safety and efficacy of CER in subjects with muscle spasms.			
Primary Objectives: The primary objective of this study is to assess the effect of CER 15 mg once daily in subjects with muscle spasms associated with musculoskeletal conditions.			
Secondary Objectives: The secondary objective for this study is to assess effect on subject rating parameters of CER 15 mg once daily.			
Additional Objectives Safety objective The safety objective for this study is to assess the safety and tolerability of CER 15 mg once daily.			
Subject Population: Males and females aged 18 to 50 years inclusive, experiencing cervical or lower back pain (as assessed by the subject) due to muscle spasms (confirmed by the physician) for no more than 14 days.			
Number of Subjects: Total number of patients to be randomized is 180: 90 into Placebo group and 90 into CER 15 mg group		Number of Sites: Approximately 10 sites in Russian Federation will be included	
Dose Level(s): <ul style="list-style-type: none"> Cyclobenzaprine HCl Extended Release, 15 mg, once daily Placebo of Cyclobenzaprine HCl Extended Release, once daily 		Route of Administration: Oral	
Duration of Treatment: 14 days		Period of Evaluation: Screening period - ≤5 days Treatment period – 14 days Follow up period – 21 days Total evaluation period is 35-40 days	
Main Criteria for Inclusion: <ol style="list-style-type: none"> In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures. The Subject is experiencing for no more than 14 days cervical and/or lower back pain (as assessed by the subject) due to muscle spasms (confirmed by the physician) associated with musculoskeletal conditions (codes M54.2 Cervicalgia and/or M54.5 Low back pain according to ICD-10). The subject is male or female and aged 18 to 50 years, inclusive. Female subjects require to be either 2 years postmenopausal or surgically sterile by bilateral tubal ligation, 			

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hysterectomy, or bilateral oophorectomy, or, if premenopausal, had to be using an approved contraceptive method.

6. Female subjects of child-bearing potential must have a negative urine human chorionic gonadotropin (hCG) test result for pregnancy at study entry.
7. After signing the informed consent form, the subject agrees not to make changes to dietary, exercise, or smoking habits and not to enter a weight loss program during his/her participation in the study.

Main Criteria for Exclusion:

1. The subject has muscular pain secondary to acute trauma or fractures (e.g., due to osteoporosis). Such conditions could have been ruled out based on medical history, x-ray, or physical examination;
2. The subject suffers from muscle spasms/pain related to polymyalgia rheumatica or ankylosing spondylitis (Bekhterev's disease). Such conditions could have been ruled out based on medical history, x-ray, or physical examination;
3. The subject has received any investigational compound within 30 days prior to Screening;
4. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period;
5. The subject has a history of drug abuse or recent (within the last 12 months) history of excessive alcohol consumption defined as >2 drinks/day (>3 oz of 80 proof alcohol or equivalent);
6. Patients with mild, moderate, severe liver impairment;
7. The subject is a study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study or may consent under duress;
8. The subject takes any concomitant medication including over-the-counter and herbal products for muscle spasms. If a subject is taking such medications, the medications has to be discontinued before starting the study;
9. The subject takes or took within last 14 days medications, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), MAO inhibitors, tramadol, bupropion, meperidine, verapamil, topical, anti-inflammatory medications;
10. The subject takes or took within last 3 days medications, such as non-steroid anti-inflammatory drugs (NSAIDs), intramuscular vitamin injections containing anaesthetics (such as vitamin Milgamma);
11. The subject has a history or clinical manifestations of significant medical condition, such as: hyperthyroidism, acute recovery phase of myocardial infarction, arrhythmias, heart block or conduction disturbances, congestive heart failure, angle-closure glaucoma, urinary retention, increased intraocular pressure.
12. The subject has a known history of positive screen for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody.
13. The subject has a history of malignant disease within 5 years prior to Screening.
14. Drug abuse in anamnesis

Main Criteria for Evaluation and Analyses:

The primary endpoints for this study are:

- The percentage of subjects with subject's rating of medication helpfulness impression on Day 3 of treatment.

Secondary endpoints for this study are:

- The percentage of subjects with physician's clinical global assessment on Day 3 of treatment.
- The percentage of subjects with subject's rating of medication helpfulness impression on Day 7 and 14 of treatment.
- The percentage of subjects with physician's clinical global assessment on Day 7 and Day 15.
- The percentage of subjects with subject-rated global impression (relief from local pain, restriction in activities of daily living, restriction of movement, intensity of local pain) of on Day 3, 7 and 14 of treatment.
- The percentage of subjects defined as responders on Day 3, 7 and 14 of treatment.

- The percentage of subjects with physician rated assessment of presence of muscle spasm, presence of local pain, limitation of range of motion, limitation of activities of daily living on Day 3, 7 and 15.

Additional Endpoints

Safety Endpoints

- AEs.
- Clinical laboratory tests (hematology, serum chemistry and urinalysis).
- Vital sign measurements (weight, blood pressure, and heart rate).
- 12-lead electrocardiogram (ECG).

Exploratory Endpoints

- Company Confidential Information
- Company Confidential Information
- Company Confidential Information

Statistical Considerations:

For the primary efficacy analysis, the subject's rating of medication helpfulness at Day 3 will be analyzed for the difference between the Placebo and the 15mg CER treatment group using a 2-sample Wilcoxon rank sum test.

A supportive analysis on responders will be done to confirm the results of the primary analysis. A continuity-adjusted Chi-square test will be used to compare the number of "responders" between the Placebo and the CER treatment group. The number and percent of subjects who met the definition of responder at Day 3 will be presented.

The primary analysis and supportive analysis will be repeated for day 7 and day 14.

The secondary efficacy analysis on the subject's rating of medication helpfulness at Day 3, Day 7 and Day 14 and physician's clinical global assessment at Day 3, Day 7 and Day 15 will be repeated using the methods described for the primary efficacy analysis and supportive analysis.

Sample Size Justification:

A sample size of at least 77 subjects in each treatment group (total of 154 subjects) is needed to detect a difference between Placebo and CER 15 mg in subject's rating of medication helpfulness impression, using a 2-sample Wilcoxon rank sum test with 80% power at a 2-sided significance level of 0.05. The assumed difference to be detected is based on the observed distribution of the ordinaly scored rating scale for the respective treatment groups in study 1106. Assuming a 15% dropout rate, 90 subjects in each treatment group (total of 180 subjects) will be randomized.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CER	Cyclobenzaprine HCl Extended Release
CNS	central nervous system
(e)CRF	case report form (electronic or paper)
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
GCDT	Global Clinical Development Team
GCP	Good Clinical Practice
GGT	γ -glutamyl transferase
hCG	human chorionic gonadotropin
HCl	hydrochloride
HIV	human immunodeficiency virus
ICD-10	International Classification of Diseases, 10 th revision
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function tests
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	nonsteroidal anti-inflammatory drugs
PTE	pretreatment event
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SNRIs	serotonin norepinephrine reuptake inhibitors
SOP	standard operating procedure
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
ULN	upper limit of normal
USP	United States Pharmacopeia
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Neck or back pain due to muscle spasms may occur at almost any time during the life cycle.

Chronic persistent low back and neck pain is seen in 25% to 60% of patients, one-year or longer after the initial episode. Spinal pain is associated with significant economic, societal, and health impact. Chronic pain syndrome has been defined as a complex condition with physical, psychological, emotional, and social components. The prevalence of chronic pain in the adult population ranges from 2% to 40%, with a median point prevalence of 15%. [Manchikanti, L; Singh, V; Datta, S; Cohen, SP; Hirsch, JA; American Society of Interventional Pain, Physicians (Jul–Aug 2009). "Comprehensive review of epidemiology, scope, and impact of spinal pain." Pain physician 12 (4): E35–70. PMID 19668291].

Cyclobenzaprine hydrochloride (HCl) is a centrally acting skeletal muscle relaxant closely related to the tricyclic antidepressants that acts mainly on the brainstem to decrease tonic somatic motor activity. Some activity at spinal cord sites may also contribute to its therapeutic effects. It is used as an adjunct treatment for relief of muscle spasm associated with musculoskeletal conditions. Cyclobenzaprine may also provide relief in a small percentage of patients with fibromyalgia. Following oral administration, its effects begin within one hour and the effects of a single dose last as long as 12 to 24 hours.

4.2 Rationale for the Proposed Study

Muscular tonic syndromes mostly occur in overstrained muscles. Patients with muscular tonic syndrome usually complain of pain either in spine or in shoulder and pelvic girdle muscles (in the lower back, neck, and shoulder). Pain usually decreases after rest, kneading and stretching the muscles. Muscular tonic syndrome can perform sanogenetic function, protecting the affected area from further damage. However, long-term persistent muscle spasm leads to negative consequences such as increased load on bony and ligamentous structures that accelerates the development of degenerative changes in the skeletal system. It can also lead to a transformation from muscular tonic syndrome to myofascial pain syndrome.

The main feature of myofascial pain syndrome is the presence of trigger point (s) - the site of local muscle gelosis. Its stimulation causes local tenderness and irradiation of the pain. Trigger points can resolve spontaneously in the absence of supporting factors. On the contrary, preserving the original exposure pathogenic factor contributes to the formation of secondary triggers, and an increase in area of pain.

In the treatment of muscular tonic pain the main role belongs to local interventions aimed at muscle relaxation or at the "destruction" of trigger points in case of myofascial pain syndrome. An effective pain control can significantly reduce the therapy terms and the use of NSAIDs, among others, is a common method of myofascial pain relieve. However their usage can be insufficient as they don't affect the spasm itself.

Muscle relaxants can be a substantial aid for muscular tonic and myofascial pain syndromes treatment as they reduce the intensity of pain, decrease painful muscle tension and improve physical activity. Pain caused by involvement of the intervertebral discs, the facet joints of the spine, muscles and other reasons increases the activity of the cord motor neurons. That results in muscle spasm, which plays a significant role in the maintenance of the pain syndrome. Pathologically increased muscle tone has various mechanisms to enhance pain: direct stimulation of pain receptors in the muscles or deterioration of muscles blood supply. These result in a vicious circle, leading to the muscle spasm and associated pain aggravation. Muscle relaxants break the "pain - muscle spasm - pain" circle and therefore are able to accelerate the convalescence process. [Danilov, A.; Russian Medical Journal, 2010, #1]. Myorix is one of the muscle relaxants that can be used for treatment of pain associated with muscle spasms.

Russian Federal Law #61-FZ (dated 12-Apr-2010) "About circulation of medicinal agents" requires that all new for Russian market pharmaceutical products for medical use should undergo clinical trials on Russian Federation territory before their registration. The Law allows not to conduct clinical trial for registration purposes if the Russian Federation was included previously in international multicentre clinical trials which have been conducted for the product.

The main purpose of this study is to explore the efficacy and safety of Cyclobenzaprine 15 mg once daily in the treatment of acute cervical and/or lower back pain due to muscle spasms of local origin in Russian patients and to provide clinical trial data for Cyclobenzaprine market registration in Russian Federation.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to assess the effect of CER 15 mg once daily in subjects with muscle spasms associated with musculoskeletal conditions.

5.1.2 Secondary Objective

The secondary objective of this study is to assess the effect on subject rating parameters of CER 15 mg once daily.

5.1.3 Additional Objectives

Safety objective

The safety objective for this study is to assess the safety and tolerability of CER 15 mg once daily.

5.2 Endpoints

5.2.1 Primary Endpoints

- The percentage of subjects with subject's rating of medication helpfulness impression on Day 3 of treatment.

5.2.2 Secondary Endpoints

- The percentage of subjects with physician's clinical global assessment on Day 3 of treatment.
- The percentage of subjects with subject's rating of medication helpfulness impression on Day 7 and 14 of treatment.
- The percentage of subjects with physician's clinical global assessment on Day 7 and 15 of treatment.
- The percentage of subjects with subject-rated global impression (relief from local pain, restriction in activities of daily living, restriction of movement, intensity of local pain) of on Day 3, 7 and 14 of treatment.
- The percentage of subjects defined as responders on Day 3, 7 and 14 of treatment.
- The percentage of subjects with physician rated assessment of presence of muscle spasm, presence of local pain, limitation of range of motion, limitation of activities of daily living on Day 3, 7 and 15.

5.2.3 Additional Endpoints

Safety Endpoints

- AEs.
- Clinical laboratory tests (hematology, serum chemistry and urinalysis).
- Vital sign measurements (weight, blood pressure, and heart rate).
- 12-lead electrocardiogram (ECG).

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Exploratory Endpoints

- Personal Protected Data
- 

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This study is:

- Phase IIIb (registration in Russian Federation)
- Safety/Efficacy Study trend
- Randomized, double-blind, placebo-controlled, parallel-group 2-arm study

Randomization ratio 1:1

Subject population - males and females aged 18 to 50 years inclusive, experiencing for no more than 14 days cervical or lower back pain (as assessed by the subject) due to muscle spasms (confirmed by the physician) associated with musculoskeletal conditions will be included to the study.

Approximately 180 subjects will be randomized in approximately 10 sites in Russian Federation

The study consists of three periods with five consecutive visits and a follow up phone call:

Screening period - ≤ 5 days prior Randomization (Screening visit)

Treatment period – 14 days (Visit 1 (Randomization), Visit 2 (Day 3), Visit 3 (Day 7), Final Visit/Study Termination (Day 15))

Follow up period – 21 days (Follow up phone call)

Total participation period for a subject will be approximately 35-40 days.

Procedures:

At each visit vital signs will be monitored and the following efficacy variables will be assessed: subject's rating of medication helpfulness, physician's clinical global assessment, subject-rated relief from local pain due to the muscle spasm, subject-rated clinical global impression of change, restriction in activities of daily living, restriction of movement, Company Confidential Information

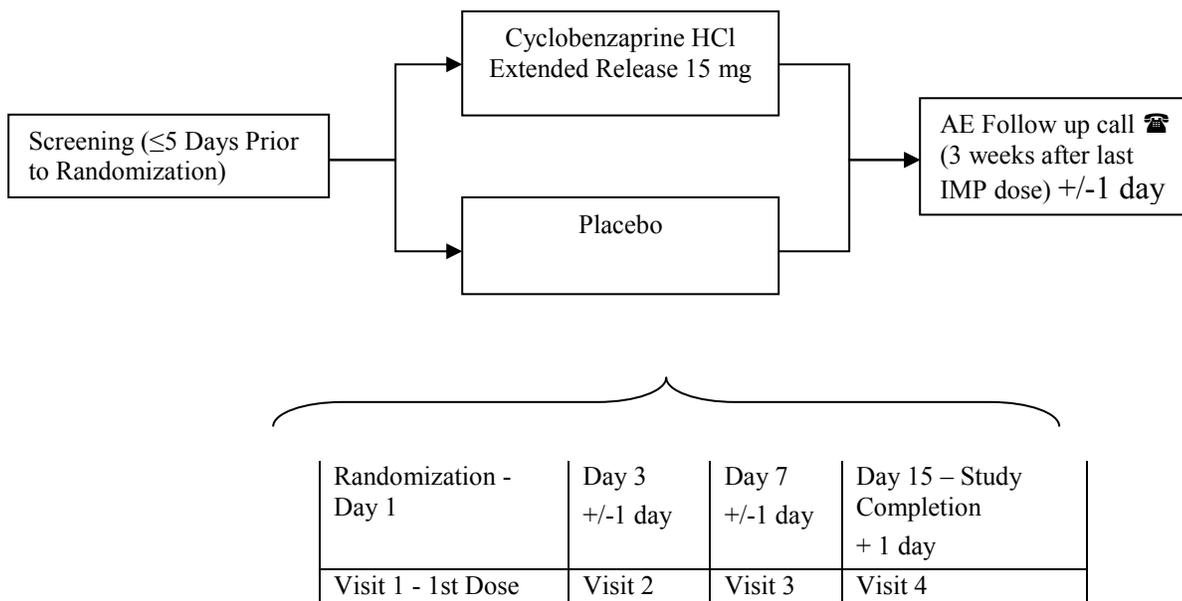
ECG, blood and urinary laboratory tests will be done on Screening and Study termination.
Any AEs if reported will be recorded.

Treatment:

- 1 capsule containing 15 mg of Cyclobenzaprine HCl Modified-Release, orally, once daily
or
- 1 capsule of Placebo of Cyclobenzaprine HCl Modified-Release, orally, once daily

Subjects will be informed that the study medication might impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

- Study design including primary and secondary criteria for evaluation and methods of measurement will be similar to previous pivotal Cyclobenzaprine studies in order to determine positive efficacy trend of Cyclobenzaprine 15 mg versus Placebo;
- The randomized, double-blind, parallel, placebo-controlled design will reduce bias in different treatment regimens with respect to efficacy and safety. Randomization will provide maximum assurance that subject characteristics are similar across the treatment groups. Blinding subjects and all study personnel who will be involved in their assessment to the study treatment will maintain the objectivity of the assessment;
- A placebo arm has been added, since the primary endpoint is a subjective score and the placebo control allows to better evaluate the treatment effect of Cyclobenzaprine;
- A placebo arm is acceptable because the study is of short duration and the cervical and/or lower back pain due to muscle spasms is not considered a life-threatening condition if untreated. Moreover, rescue therapy will be implemented in lack of efficacy cases before subject is discontinued from the study;
- The dose level of Cyclobenzaprine 15 mg once daily is chosen for this study as the approved dose for the treatment of the pain due to muscle spasms of local origin. The Cyclobenzaprine 15 mg once daily has shown its efficacious and safe in adult patients with the pain due to muscle spasms, so it is expected that the same dose will be effective and safe in Russian patients.

The endpoint assessment for this study will take place on Day 3 instead of Day 4 (as utilized in 1105 and 1106 studies) which is based on cyclobenzaprine MR 30 mg pharmacokinetic parameters T_{max}

= 10.5 ± 3.32 hours and $t_{1/2} = 27.7 \pm 8.56$ hours and implies capturing probable earlier clinical effects of the drug than it was shown in previous studies.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for Cyclobenzaprin HCl, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The Subject is experiencing for no more than 14 days cervical and/or lower back pain (as assessed by the subject) due to muscle spasms (confirmed by the physician) associated with musculoskeletal conditions (defined by codes M54.2 Cervicalgia and/or M54.5 Low back pain according to ICD-10).
4. The subject is male or female and aged 18 to 50 years, inclusive.
5. Female subjects require to be either 2 years postmenopausal or surgically sterile by bilateral tubal ligation, hysterectomy, or bilateral oophorectomy, or, if premenopausal, had to be using an approved contraceptive method*.

*Definitions and acceptable methods of contraception are defined in Section ~~9.1.109-1.10~~ Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section ~~9.1.119-1.11~~ Pregnancy.

6. Female subjects of child-bearing potential must have a negative urine human chorionic gonadotropin (hCG) test result for pregnancy at study entry.
7. After signing the informed consent form, the subject agrees not to make changes to dietary, exercise, or smoking habits and not to enter a weight loss program during his/her participation in the study.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has muscular pain secondary to acute trauma or fractures (e.g., due to osteoporosis). Such conditions could have been ruled out based on medical history, x-ray, or physical examination.
2. The subject suffers from muscle spasms/pain related to polymyalgia rheumatica or ankylosing spondylitis (Bekhterev's disease). Such conditions could have been ruled out based on medical history, x-ray, or physical examination;
3. The subject has received any investigational compound within 30 days prior to Screening.
4. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.

5. The subject has a history of drug abuse or recent (within the last 12 months) history of excessive alcohol consumption defined as >2 drinks/day (>3 oz of 80 proof alcohol or equivalent).
6. Patients with mild, moderate, severe liver impairment.
7. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
8. The subject takes any concomitant medication including over-the-counter and herbal products for muscle spasms. If a subject is taking such medications, the medications has to be discontinued before starting the study.
9. The subject takes or took within last 14 days medications, such as:
 - a. selective serotonin reuptake inhibitors (SSRIs);
 - b. serotonin norepinephrine reuptake inhibitors (SNRIs);
 - c. tricyclic antidepressants (TCAs);
 - d. MAO inhibitors;
 - e. tramadol;
 - f. bupropion;
 - g. meperidine;
 - h. verapamil; topical anti-inflammatory medications, including patches
 - i. paracetamol
 - j. opioid analgesics
10. The subject takes or took within last 3 days medications, such as:
 - a. non-steroid anti-inflammatory drugs (NSAIDs);
 - b. Intramuscular vitamin injections containing anaesthetics (such as vitamin Milgamma).
11. The subject has a history or clinical manifestations of significant medical condition, such as:
 - a. hyperthyroidism;
 - b. acute recovery phase of myocardial infarction;
 - c. arrhythmias, heart block or conduction disturbances;
 - d. congestive heart failure;
 - e. angle-closure glaucoma;
 - f. urinary retention;
 - g. increased intraocular pressure.
12. The subject has abnormal physical findings or a medical condition that might have placed the subject at risk or interfered with the subject's ability to participate in the study.

13. The subject has any known condition or disorder that might have affected absorption of the study drug.
14. The subject has a history of hypersensitivity or allergies to cyclobenzaprine and/or tricyclic antidepressants or any of their components.
15. The subject has a history of hypersensitivity to any NSAIDs including salicylate sensitivity.
16. The subject has a history of thrombocytopenia.
17. The subject has a history of gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders.
18. The subject had active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
19. The subject has a history of severe renal impairment
20. The subject had a major surgery during the 6 months preceding study entry.
21. The subject has a language barrier or any other problems precluding good communication or cooperation.
22. The subject has any reason to believe that he/she would not be able to complete the evaluations needed in this study.
23. The subject has a known history of positive screen for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody.
24. The subject has a history of malignant disease within 5 years prior to Screening.
25. Drug abuse in anamnesis

7.3 Excluded Medications and Treatments

Drug Class	Disallowed Prior to Screening	Disallowed During the Study for		
		Chronic Use	Episodic Use	Comments or Exceptions
Analgesics				Concomitant use of Cyclobenzaprine with listed medications can lead to a potentially life-threatening serotonin syndrome and /or affect the study results.
• tramadol	14 days	+	+*	
• meperidine	14 days	+	+*	
• paracetamol	14 days	+	+*	
• opioid analgesics	14 days	+	+*	
Antiarrhythmics				
• verapamil	14 days	+	+	

Antidepressants <ul style="list-style-type: none"> • selective serotonin reuptake inhibitors • serotonin norepinephrine reuptake inhibitors • tricyclic antidepressants • MAO inhibitors • Bupropion 	14 days	+	+	
	14 days	+	+	
	14 days	+	+	
	14 days	+	+	
	14 days	+	+	
<ul style="list-style-type: none"> • Topical anti-inflammatory medications (including patches) 	14 days	+	+*	
<ul style="list-style-type: none"> • NSAIDs • intramuscular vitamin injections containing anaesthetics (such as Milgamma) 	3 days	+	+*	
	3 days	+	+	

*Analgesics will be allowed only as add-on rescue therapy, to be used before the subject is discontinued due to lack of efficacy.

Subjects will be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Medications necessary for the well-being of the subject will be allowed during the study.

7.4 Diet, Fluid, Activity Control and Treatment Facilities

The subject will be asked not to make changes to dietary, exercise, or smoking habits and not to enter a weight loss program during his/her participation in the study. Subjects will be warned that cyclobenzaprine, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 9.1.12.

1. Pretreatment event (PTE) or adverse event (AE). The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

- Liver Function Test (LFT) Abnormalities

Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if the following circumstances occur at any time during study medication treatment:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>8 \times$ upper limit of normal (ULN), or
- ALT or AST $>5 \times$ ULN and persists for more than 2 weeks, or
- ALT or AST $>3 \times$ ULN in conjunction with elevated total bilirubin $>2 \times$ ULN or international normalized ratio (INR) >1.5 , or
- ALT or AST $>3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($>5\%$).

2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. Lack of efficacy. The necessity to use rescue medication (any analgesics) AND/OR the investigator has determined that the subject is not benefiting from investigational treatment and, continued participation would pose an unacceptable risk to the subject.

8. Other.

Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

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7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

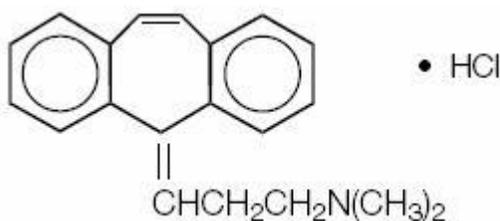
This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Investigational drug

Cyclobenzaprine HCl is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in Cyclobenzaprine HCl extended-release capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HCl) is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N \cdot HCl$ and a molecular weight of 311.9. It has a melting point of $217^{\circ}C$, and a pK_a of 8.47 at $25^{\circ}C$. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(5*H*-dibenzo[*a,d*] cyclohepten-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



Cyclobenzaprine HCl capsules contain the following inactive ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry[®] Clear YS-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide. Cyclobenzaprine HCl 15 mg capsules also contain D&C yellow #10, FD&C green #3, and FD&C red #40.

The detailed information about the Drug, including list of AE is presented in the Protocol Appendix E.

8.1.1.2 Rescue Medication

NSAIDs, topical over-the-counter medications and other analgesics will be allowed as rescue therapy only and to be used before the subject is discontinued due to lack of efficacy.

8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

Cyclobenzaprine ER (CER) 15 mg and Placebo will be supplied to the study sites as identical, similar size, opaque, white capsules packed into 40 cubic centimeters High Density Polyethylene bottles, containing 60 capsules. To avoid any overdose each study subjects will receive one 40 cubic centimeters High Density Polyethylene bottles, containing 20 capsules with CER 15 mg or Placebo,

according to their randomized treatment assignment according to the procedure outlined in Section 9.3.2.

8.1.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
		Active	Placebo
A	Placebo QD	N/A	1 capsule of placebo, orally
B	Cyclobenzaprine 15 mg QD	1 capsule containing 15 mg of Cyclobenzaprine HCl Modified-Release, orally	N/A

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated in accordance with the compound-specific instructions.

All of the cases of cyclobenzaprine HCl overdose which were reported to five regional poison centers were reviewed for the years 1989 to 1993. A total of 750 charts were identified with cyclobenzaprine HCl exposure; and of these, 523 charts had sufficient data for evaluation. There were 121 cases in which multiple drugs were involved, and 402 cases involving only the ingestion of cyclobenzaprine HCl. The ages of the patients ranged from 7 months to 77 years with a mean of 20 years; and children

6-years-old or younger comprised 26% of the overdose cases. Overall, 63% of the patients were females.

None of the overdosed patients died. The most common adverse effects were lethargy, sinus tachycardia, and agitation. Both hypertension and hypotension were observed. Other than sinus tachycardia, dysrhythmias occurred infrequently; and none were life-threatening. No seizures occurred. In situations where the times of ingestion were known, any symptoms of overdose were manifested within 4 hours. The ingested doses of cyclobenzaprine HCl ranged from 5 mg to 1000 mg with a mean of 133 mg. The mean dose of cyclobenzaprine HCl ingested by asymptomatic patients was 45 mg, and the mean dose of cyclobenzaprine HCl ingested by symptomatic patients was 183 mg [Spiller HA, Winter ML, Mann KV, Borys DJ, Muir S, Krenzlok EP. Five-year multicenter retrospective review of cyclobenzaprine toxicity. *J Emerg Med.* 1995 Nov-Dec;13(6):781-5.].

Treatment

Treatment for overdose primarily involved symptomatic and supportive care. Rapid decontamination of the gastrointestinal tract was required. The other types of therapies used included mechanical ventilation, treatment with dopamine, the administration of a fluid bolus, sedation, and Foley catheterization. Overdoses with less than 100 mg of cyclobenzaprine HCl did not require treatment beyond gastrointestinal decontamination. Therefore, the recommended treatment for cyclobenzaprine HCl overdose begins with emptying the stomach as quickly as possible by emesis followed by gastric lavage. After gastric lavage, activated charcoal may be administered. Twenty grams to 30 g of activated charcoal may be given every 4 to 6 hours during the first 24 to 48 hours after ingestion. An electrocardiogram should be taken, and close monitoring of cardiac function must be instituted if there is any evidence of dysrhythmia. Maintenance of an open airway, adequate fluid intake, and regulation of body temperature are necessary.

The intravenous administration of 1 mg to 3 mg of physostigmine salicylate is reported to reverse symptoms of poisoning by atropine and other drugs with anticholinergic activity; therefore, physostigmine may be helpful in the treatment of cyclobenzaprine HCl overdose. Because physostigmine is rapidly metabolized, the dosage should be repeated as required, particularly if life-threatening signs, such as arrhythmias, convulsions, and deep coma recur or persist after the initial dose of physostigmine.

Because physostigmine itself may be toxic, it is not recommended for routine use.⁶ Standard medical measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. When signs of cardiac failure occur, the use of a short-acting digitalis preparation should be considered. Close monitoring of cardiac function for not less than five days is advisable.

Anticonvulsants may be given to control seizures. Dialysis is probably of no value because of the low plasma concentrations of cyclobenzaprine HCl. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

In conclusion, cyclobenzaprine HCl does not appear to produce the life-threatening cardiovascular or neurologic effects of the cyclic antidepressants in doses less than 1 g. Lethargy and anticholinergic effects are prominent, though serious toxicity is infrequent.

8.2 Investigational drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the schedule allocated to each study site.

After ICF signing the investigator or investigator's designee will access the IVRS/IWRS to obtain the subject study number.

The investigator or the investigator's designee will utilize the IVRS/IWRS to randomize the subject into the study. The medication identification (ID) number of the investigational drug will then be provided by the IVRS/IWRS. The investigational drug will be dispensed on the Baseline visit.

8.3 Randomization Code Creation and Storage

The randomization code will be assigned via IVRS/IWRS.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IVRS/IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IVRS/IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the (e)CRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (Cyclobenzaprin or placebo), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and sending by e-mail per instructions provided at site initiation visit. If there are any discrepancies between the

packing list versus the actual product received, Takeda and/or its designee must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs, received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for each Medication ID number received / dispensed at the site.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IVRS/IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race as described by the subject, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 14 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other (if applicable). All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

9.1.5 Vital Sign Procedure

Vital signs will include sitting blood pressure (resting more than 5 minutes), and pulse (bpm).

9.1.6 Primary Efficacy Measurement

The measures of effectiveness in this study will include:

- **Subject's rating of medication helpfulness:**

Subjects will be asked to assess it on a daily basis (in the daily diary), using the following 5-point rating scale: "How would you rate this study medication in improving your condition?"

"0 = poor"

"1 = fair"

"2 = good"

"3 = very good"

"4 = excellent"

Assessment of the subject's answers will be made for the Day 3, 7 and 15.

- **Physician's clinical global assessment :**

The investigator will be asked to assess their clinical global impression of change compared to Baseline, based on physical examination, degree of muscle spasm (presence of muscle spasm assessment), reaction to palpation (presence of local pain assessment), limitation of range of motion, and evaluation of the patient's reported functional assessment (limitation of activities of daily living assessment). The following 5-point rating scale will be used:

"1 = worse"

"2 = no change"

"3 = slight improvement"

"4 = moderate improvement"

"5 = marked improvement"

Assessment will be made for the Day 3, 7 and 15.

- **The subject-rated relief from local pain:**

Subjects will be asked to assess on a daily basis (in the daily diary) their level of relief from local pain due to the muscle spasm (in either the lower back or cervical spine) compared to Baseline (Visit 1) using the following 5-point rating scale:

"1 = no relief"

"2 = a little relief"

"3 = some relief"

"4 = a lot of relief"

"5 = complete relief"

Assessment of the subject's answers will be made for the Day 3, 7 and 15.

- **The subject-rated restriction in activities of daily living:**

Subjects will be asked to assess on a daily basis (in the daily diary) the change in the severity of restriction in the activities of daily living compared to Baseline (Visit 1) using the following 5-point rating scale:

"1 = worsening"

"2 = no change"

"3 = mild improvement:"

"4 = moderate improvement"

"5 = marked improvement"

Assessment of the subject's answers will be made for the Day 3, 7 and 15.

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- **The subject-rated restriction of movement:**

Subjects will be asked to assess on a daily basis (in the daily diary), the change in restriction of movement due to the muscle spasm compared to Baseline (Visit 1) using the following 5-point rating scale:

“1 = no relief”

“2 = a little relief”

“3 = some relief”

“4 = a lot of relief”

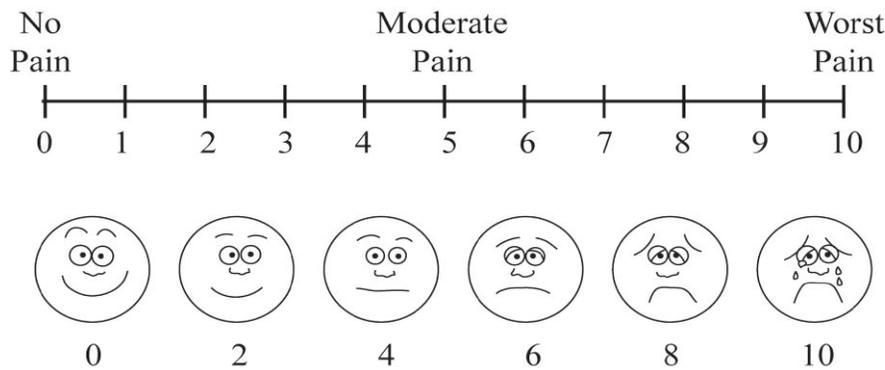
“5 = complete relief”

Assessment of the subject’s answers will be made for the Day 3, 7 and 15.

- **The subject-rated intensity of local pain:**

Subjects will be asked to assess on a daily basis (in the daily diary) their intensity of local pain due to the muscle spasm (in either the lower back or cervical spine) using the following digital rating scale. It is necessary to mark the intensity of pain by circling a one of the 11 points from 0 "No Pain" to 10 "Severe Pain" with an intermediate value of 5 - "Moderate Pain".

Facial pain scale is presented to help the patient to identify the primary area of the intensity of the pain experienced:



Assessment of the subject’s answers will be made for the Day 3, 7 and 15.

- **Subject-Rated Clinical Global Impression:**

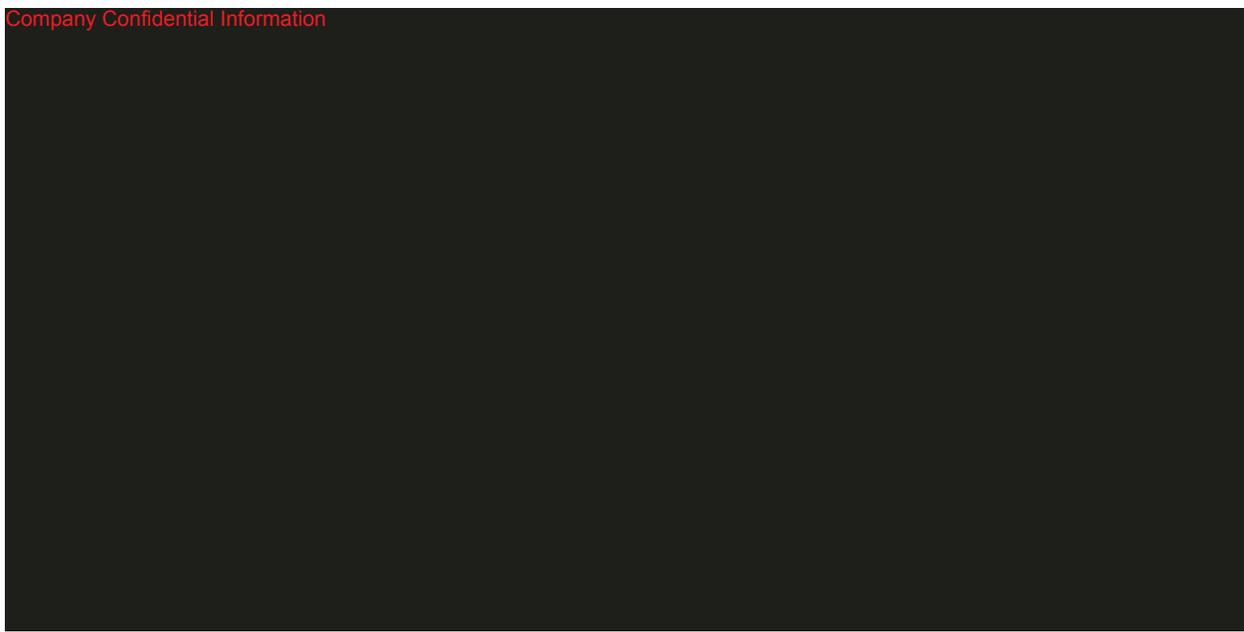
Subjects will be asked to assess on a daily basis (in the daily diary) their clinical global impression of change compared to Baseline, based on rating on medication helpfulness, relief from local pain, restriction in activities of daily living, restriction of movement.

Assessment of the subject’s answers will be made for the Day 3, 7 and 15.

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- Hematology, blood chemistry, urinalysis, urine pregnancy testing (if applicable), vital signs, physical examinations, and ECGs will be performed at Screening and study termination. Vital signs will be recorded at each clinic visit. Monitoring and recording of AEs will be performed during each clinic visit and continued for 3 weeks after the last dose of study drug.

Other assessments:

- **Presence of muscle spasm**

The physician was asked to evaluate the presence of muscle spasm by palpation (increased consistency of a muscle or group of muscles) using the following 5-point rating scale at each visit:

“1 = none” (no muscle spasm present)

“2 = mild” (the muscle is somewhat harder than usual)

“3 = moderate” (muscles are hard and borders of increased consistency can be determined by palpation)

“4 = moderately severe” (muscles are very hard and borders are sharply defined by palpation)

“5 = severe” (board-like hardness of the muscles)

- **Presence of local pain**

The physician was asked to assess the presence of local pain due to muscle spasm by palpation (tenderness on palpation) using the following 5-point rating scale at each visit:

“1 = none” (no pain)

“2 = mild” (complaint of local discomfort on palpation)

“3 = moderate” (objective evidence that the area is painful, such as defensive movements, reflex dilatation of pupils, etc.)

“4 = moderately severe” (the area is very painful)

“5 = severe” (the area is intolerably painful and subject objects to the examination)

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- **Limitation of range of motion**

The physician was asked to assess at each visit, the subject's limitation of range of motion using the following 5-point rating scale:

"1 = none" (no limitation in range of motion)

"2 = mild" (restriction of the normal motion by 10-15%)

"3 = moderate" (restriction of the motion by no more than 50%)

"4 = moderately severe" (restriction of the expected motion by no more than 80%)

"5 = severe" (the subject has great difficulty in attempting to perform one or more of the major motions)

- **Limitation of activities of daily living**

The physician was asked to assess by both direct observation and historical questioning, the limitation of activities of daily living using the following 5-point rating scale at each visit:

"1 = none" (no limitation of activities of daily living)

"2 = mild" (the subject is able to perform his customary tasks, but with discomfort)

"3 = moderate" (the subject is able to perform partially with discomfort some essential tasks and activities)

"4 = moderately severe" (the subject performs partially with great difficulty some essential tasks and activities)

"5 = severe" (the subject is unable to perform most of the essential tasks or activities)

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at screening examination. The condition (ie, diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 10 mL, and the approximate total volume of blood for the study is 20 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC)	Alanine aminotransferase	pH
White blood cells (WBC)	Albumin	Protein
Hemoglobin	Alkaline phosphatase	
	Aspartate aminotransferase	
Other:		
Urine		
hCG for pregnancy (only for female subjects of childbearing potential)		

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST $>3 \times$ ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST $>3 \times$ ULN in conjunction with total bilirubin $>2 \times$ ULN.)

If the ALT or AST remains elevated $>3 \times$ ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

The investigator or designee is responsible for transcribing or attaching laboratory results to the (e)CRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 3 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent (for oral contraceptives – for at least 90 days prior to Screening), throughout the duration of the study, and for 3 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 2 years since last regular

menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study the acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.
- #Progesterone T PLUS condom or spermicide.

Hormonal contraceptives*:**

- Implants.
- Hormone shot/injection.
- Combined pill.
- Minipill.
- Patch.
- Vaginal ring PLUS male condom and spermicide.

***In case oral contraceptives are used for less than 90 days before screening barrier methods should be used in addition to oral contraceptives.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures ([Appendix A](#)).

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after Visit 1 or within 21 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she

became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

A standard 12-lead ECG will be recorded at Screening and Study termination. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

9.1.13 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this visit, the investigator should complete the (e)CRF. The data to be collected in CRF for Screen Failures as a minimum: Subject Number and Initials, Date of Informed consent, Demographics data, Inclusion/Exclusion criteria, PTEs/SAEs, Date of Screen failure.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.14 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable (e)CRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring the dispensed study medication bottle to each site visit.

Treatment compliance will be checked by Investigator at Visits 2, and 3. In case of compliance deviation all subjects should be reinstructed about the dosing requirement during study contacts. The

authorized study personnel conducting the re-education must document the process in the subject source records.

Treatment compliance for entire treatment period will be calculated at V4 using the formula:

Compliance in % = (# tablets taken during treatment period / # tablets to be taken during treatment period)*100

Any noncompliance from the administered dose must be documented as protocol deviation.

If treatment compliance is outside of 70% - 130% ranges for the entire treatment period, it should be reported as significant protocol deviation.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects will be screened within ≤ 5 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.12 for procedures for documenting screening failures.

Procedures to be completed at Screening include:

- Informed consent.
- Demographics, medical history and medication history.
- Physical examination.
- Vital signs.
- Weight.
- Height
- ECG procedure.
- Concomitant medications.
- Concurrent medical conditions.
- Collection of blood and urine samples for hematology, serum chemistry, urine pregnancy testing (if applicable), and urinalysis.
- Assessment of Inclusion/Exclusion Criteria
- Pre-Treatment Events

9.3.2 Randomization

Randomization will take place on Day1 (could be the same day at which Screening visit took place). The following procedures will be performed and documented during Randomization:

- Vital Signs (if not same day as Screening procedures).
- Concomitant medications.
- Adverse Events.
- The following parameters will be assessed by the investigator: presence of muscle spasm, presence of local pain, limitation of activities of daily living, and limitation of range of motion.
- Subject Diary dispense. Subjects should be instructed :
 - To complete assessment for Day 1 at the hospital before the first drug intake.
 - Starting from Day 2 record the following assessments (compared to Baseline) in the daily diary: rating of medication helpfulness, relief from local pain, subject-rated Clinical global impression, restriction in activities of daily living, and restriction of movement;
 - To record the following assessments in the daily diary: **Company Confidential Information** intensity of local pain **Company Confidential Information** ;
 - To complete their diary during 14 days at the same time each day if possible but record the worst feeling/symptom since the diary was last completed. No diary to be completed at Day 15 (Visit 4) but returned to the Investigator.
 - To bring their diary to each study visit for review by Investigator. Completed pages will be collected by Investigator, then the diary will be dispensed to subject again.
- If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS, as described in Section 8.2.
- Study drug dispense. The medication identification (ID) number of the study drug will be provided via IVRS/IWRS. To avoid any overdose and non-compliance with study drug intake, original bottle containing 60 capsules with CER 15 mg or Placebo will be opened in front of the subject and 40 capsules of 60 will be removed in cleanliness condition and put into the additional bottle for keeping at the site (never dispensed to subject) until destruction. Original bottle containing 20 capsules with CER 15 mg or Placebo will be dispensed to subject. Subject will be instructed to:
 - To swallow one capsule whole with 180 mL of room temperature water, once daily in the evening between 18:00 and 19:00 starting from Day1.
 - To take the study drug for 14 days, even if complete relief has been achieved earlier. The last day of study drug intake should be Day14 in the evening.
 - Not to open/crush the capsules at any time.
 - To bring all unused study medication to each study visit.
 - Subjects will be warned that the study medication might impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

9.3.3 Visit 2 (Day 3) and Visit 3 (Day 7)

Subjects will visit the clinic on Day 3 and on Day 7. The following assessments will be performed at the both visits:

- Vital Signs.
- concomitant medications.
- Adverse Events.
- The investigator will assess: presence of muscle spasm, presence of local pain, limitation of activities of daily living, and limitation of range of motion.
- Physician's clinical global assessment based on presence of muscle spasm, presence of local pain, limitation of range of motion, and limitation of activities of daily living will be recorded.
- Subject diaries will be reviewed. Completed pages will be collected by Investigator, then the diary will be dispensed to subject again.
- Study drug returned and medication compliance checked, then study drug will be dispensed again.

9.3.4 Visit 4 (Day 15) or Early Termination

The Visit 4 will be performed on Day 15 or at the Early Termination Visit. The following procedures will be performed and documented:

- Physical examination.
- Vital signs.
- Weight
- Collection of blood and urine samples for hematology, serum chemistry, urine pregnancy testing (if applicable), and urinalysis.
- Inquiry regarding any concomitant medications.
- Inquiry for Adverse Events.
- ECG procedure.
- The investigator will assess: presence of muscle spasm, presence of local pain, limitation of activities of daily living, and limitation of range of motion.
- Physician's clinical global assessment based on presence of muscle spasm, presence of local pain, limitation of range of motion, and limitation of activities of daily living was recorded.
- Subject diary collection and review.
- Unused study drug return and compliance calculation.
- For all subjects receiving study medication, the investigator must complete the End of Study (e)CRF page.

9.3.5 Follow-up call

Follow-up telephone calls will be used to monitor AEs for 3 weeks after the last dose of study drug.

9.3.6 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of...”).
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg “worsening of...”).
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the (e)CRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure Anaphylaxis

Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Visit 1) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Visit 1). Routine collection of AEs will continue 3 weeks after the last dose of study drug.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Severity.
4. Investigator’s opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

Patient diaries will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator’s name.
- Name of the study medication(s)

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- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated $>3 \times \text{ULN}$ on 2 consecutive occasions, the abnormality should be recorded as an AE. If a subject is noted to have ALT or AST $>3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section ~~10.2.2~~10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately, within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the (e)CRFs for completeness and accuracy and must sign and date the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), {copies of all paper CRFs and query responses/ electronic copy of eCRFs, including the audit trail}, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not

approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. Unblinding of subject's treatment assignment will only occur after database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The Full Analysis Set (FAS) will consist of subjects who received at least one dose of investigation product. Subjects in the FAS population will be analysed according to their original treatment assignment regardless of the treatment received.

The safety analysis set will consist of subjects who received at least one dose of investigational product. Subjects in the safety population will be analysed according to their treatment received, regardless of treatment assigned; subjects who received ≥ 1 dose of CER 15 mg will be analyzed in the CER 15 mg treatment group.

The per-protocol (PP) analysis set will consist of subjects no major protocol violations, and who received at least 1 dose of investigational product.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

All data collected in this study will, where applicable, be summarised by treatment regimen using descriptive statistics. For continuous variables mean values, standard deviations, median and lower and upper percentiles, minimum and maximum will be calculated. For categorical variables frequencies and percent will be calculated.

13.1.3 Efficacy Analysis

All efficacy analyses will be based on an FAS subject population. The primary efficacy endpoint will also be analysed using the PP subject population. Unless otherwise specified, all statistical tests will be conducted against a 2-sided alternative hypothesis at the 0.05 level of significance.

For all efficacy evaluations, if the subject discontinued the double-blind treatment phase prior to Day 15, the last available post treatment (final) evaluation was used to estimate the remaining missing evaluations (ie, last observation carried forward [LOCF]). For reference, the observed values were summarized and analyzed using the same methods as the LOCF values.

Primary Efficacy Endpoints

For the primary efficacy analysis, the subject's rating of medication helpfulness at Day 3 will be analyzed for the difference between the Placebo and the 15mg CER treatment group using a 2-sample Wilcoxon rank sum test. The primary end point is a 5-point ordinal rating scale from 0=Poor to 4=Excellent. This study will evaluate differences between Placebo and CER treatment on the percentages for each of the 5-grade scale categories. Therefore, the 2-sample Wilcoxon sum rank test

will compare the shift of ordinal distributions of responses in both treatment groups. Only differences between the treatment groups at the significance level of 0.05 will be considered statistically significant. Frequency counts and percentages showing the distribution of the subject's rating of medication helpfulness at Day 3 will be provided to summarize these parameters.

A supportive analysis on responders will be done to confirm the results of the primary analysis. A responder will be defined as a subject who had a rating of either "very good" or "excellent" for the subject's rating of medication helpfulness at Day 3. A continuity-adjusted Chi-square test will be used to compare the number of "responders" between the Placebo and the CER treatment group. The number and percent of subjects who met the definition of responder at Day 3 will be presented.

The primary analysis and supportive analysis will be repeated for day 7 and day 14.

Trends in the distribution of ratings by treatment group will be compared across the 3 visits to determine if there were any qualitative differences in the pattern of treatment response. Differences between treatments in the distribution of ratings at the 3 visits will be analysed using a weighted least squares model for marginal homogeneity including a parameter for treatment and treatment-by-visit interaction. Trends over time in the proportion of responders among the treatment groups will be assessed qualitatively by comparing the patterns of change in proportion of responders from Day 3 through Day 14. Repeated-measures analysis of proportions using Generalized Estimating Equations (GEE) will be used for comparisons among treatments of the trend in proportion of responders over time.

Time to improvement in subject's rating of medication helpfulness will be defined as the number of days from the start of treatment to the first time there was an assessment of "fair" to "excellent". If the subject did not have any improvement in their rating of medication helpfulness, time to improvement was censored and equaled the number of days from the start of treatment to the last measurement during the study. The Kaplan-Meier curves will be compared using the generalized Wilcoxon test for survival analysis.

Secondary Efficacy Endpoints

The following subject's ratings will be analyzed and summarized: relief from local pain due to muscle spasm, restriction in activities of daily living, restriction of movement, and clinical global impression. Time to improvement of subject-rated relief from local pain will be analyzed.

Subject Ratings

The subject's ratings will be analyzed separately for the differences between the Placebo and CER treatment group using a 2-sample Wilcoxon rank sum test.

Time to improvement of subject-rated relief from local pain will be defined as the number of days from the start of treatment to the first time there was an assessment of "a little relief" to "complete relief". If the subject did not have any improvement in their rating of relief from local pain, time to improvement was censored and equaled the number of days from the start of treatment to the last measurement recorded for the subject during the study. The Kaplan-Meier curves will be compared using the generalized Wilcoxon test for survival analysis.

Other Efficacy Endpoints

The physician's clinical global assessment on Days 3, 7 and 15 of treatment will be analysed in the same way as the primary endpoint.

The following physician-rated assessments will be summarized: presence of muscle spasm, presence of local pain, limitation of range of motion, and limitation of activities of daily living. Frequency counts and percentages showing the distribution of the above physician's assessments at Days 1, 3, 7, and 15 are provided to summarize these parameters.

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For efficacy evaluations, End of Study was defined as Day 15, or if the subject discontinued the double-blind treatment phase prior to Day 15, the last available post treatment evaluation was used to estimate the remaining missing evaluations (ie, LOCF).

If the assumptions underlying planned inferential methods are not adequately met, methods will be amended as needed for appropriate analysis.

13.1.4 Safety Analysis

For all safety endpoints, Baseline is defined as the last non-missing measurement prior to first dose of study drug. All safety analyses will be summarized using the safety analysis set.

13.1.4.1 AEs

All AEs will be coded by system organ class, high level term, and preferred term using MedDRA. TEAEs are defined as AEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after study drug administration. TEAEs will be summarized by treatment group and dosing frequency by system organ class and preferred term. The following summary tables will be included in the report: summary of TEAEs and drug-related TEAEs, relationship of TEAEs to study drug (related vs. not-related), severity of TEAEs and related TEAEs. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

13.1.4.2 Safety Laboratory Evaluation

Individual results of safety laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. All clinical laboratory data will be listed.

13.1.4.3 Vital Signs

Individual results of vital signs that meet Takeda's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and changes from Baseline in vital sign measurements will be summarized. All vital sign data will be provided in the data listings.

13.1.4.4 ECGs

Individual results of qualitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria will be summarized and listed. Shift tables will be generated for the investigator's ECG interpretations that changed from Baseline to the postdose collections. All ECG data will be provided in the data listings.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A sample size of at least 77 subjects in each treatment group (total of 154 subjects) is needed to detect a difference between Placebo and CER 15 mg in subject's rating of medication helpfulness impression, using a 2-sample Wilcoxon rank sum test with 80% power at a 2-sided significance level of 0.05 (Kolassa, J. E. (1995), "A Comparison of Size and Power Calculations for the Wilcoxon Statistic for Ordered Categorical Data," *Statistics in Medicine*, 14, 1577–1581). The assumed difference to be detected is based on the observed distribution of the ordinaly scored rating scale for the respective treatment groups in study 1106. Assuming a 15% dropout rate, 90 subjects in each treatment group (total of 180 subjects) will be randomized.

14.0 CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator’s final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject’s personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed

consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Relief from Local Pain ^d			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject-Rated Clinical Global Impression ^d			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Restriction in Activities of Daily Living ^d			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Restriction of Movement ^d			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Company Confidential Information																		
Dispense Diary		X		X				X										
Review Diary				X				X									X	

- a) Screening procedures will be performed within 5 days before Visit 1 (Baseline = day of randomization);
- b) Subjects who discontinued the study early should undergo study termination procedures as soon as possible;
- c) Adverse events will be monitored for 3 weeks after the last dose of study drug administration through follow-up telephone calls;
- d) These should be assessed relative to Baseline;
- e) Hematology (RBC, WBC, hemoglobin), Serum chemistry (ALT, albumin, alkaline phosphatase, AST), Urinalysis (pH, protein, if required hCG) will be done in local laboratories of the investigational site;
- f) Dispensing occurs at Day 1, 3, 7; Return and Compliance occurs at Day 3, 7, 15;
- g) Only weight measurement to be done at Termination
- h) If screening and randomization are completed on the same day, vitals signs and concomitant medication assessment only need to be completed once (and entered in the CRF as Day 1 Randomization (Baseline)).
- i) Concomitant treatments include concomitant medications

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRF, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.

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24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
- a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.
25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Instruction for Medical Use – Myorix

THE MINISTRY OF HEALTHCARE OF THE RUSSIAN FEDERATION

PATIENT INFORMATION LEAFLET

of medicinal product for medical use

Myorix[®]

Marketing authorization number:

Trade name: Myorix[®]

International non-proprietary name: Cyclobenzaprine

Dosage form: sustained-action capsules

Formulation

One sustained-action capsule contains:

15 mg dosage:

Active ingredient: cyclobenzaprine hydrochloride - 15.0 mg

Excipients: sugar grit¹ - 109.7 mg, transparent opadry[®] YS-1-7006² - 1.2 mg, ethyl cellulose - 5.4 mg, diethyl phthalate - 0.6 mg;

Capsule coat: Iron oxide red dye - 0.2379 mg, iron oxide red dye - 0.5947 mg, titanium dioxide - 0.2942 mg, water - 5.3500 mg, gelatin - 31.5232 mg.

Identification ink: blue ink TekPrint[™] SB-6018³ trace quantity

¹sugar grit content: saccharose 68.56 - 100.38 mg, corn starch 9.32 - 41.14 mg;

²Content of transparent Opadry[®] YS-1-7006: HPMC 1.091 mg, polyethylene glycol 0.109 mg;

³Content of blue ink TekPrint[™] SB-6018: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, concentrated solution of ammonium hydroxide, blue FD&C dye No. 2 aluminum lake, indigo carmine.

30 mg dosage:

Active ingredient: cyclobenzaprine hydrochloride - 30.0 mg

Excipients: sugar grit¹ - 87.6 mg, transparent opadry[®] YS-1-7006² - 2.4 mg, ethyl cellulose - 10.7 mg, diethyl phthalate - 1.2 mg;

Capsule coat: blue FD&C dye No. 2 - 0.1906 mg, blue FD&C dye No. 1 - 0.0003 mg, red FD&C dye No. 40 - 0.0245 mg, yellow FD&C dye No. 6 - 0.0348 mg, titanium dioxide - 0.4399 mg, water - 5.4100 mg, gelatin - 31.8999 mg.

Identification ink: Opacode[®] white ink S-1-7085⁴ trace quantity.

¹sugar grit content: saccharose 54.75 - 80.15 mg, corn starch 7.45 - 32.85 mg;

²Content of transparent Opadry[®] YS-1-7006: HPMC 2.182 mg, polyethylene glycol 0.218 mg;

⁴Content of Opacode[®] white ink S-1-7085: shellac Glaze-45 % in SD-45 alcohol, titanium dioxide, isopropyl alcohol, ammonium hydroxide 28 %, propylene glycol, N-butyl alcohol, simethicon.

Description

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15 mg dosage capsules.

Hard gelatin capsules with light orange to orange-brown body with blue imprint “1002-15” and light orange to orange-brown cap with blue imprint “EUR”. Capsule content - white to yellow spherical granules.

30 mg dosage capsules.

Hard gelatin capsules with blue to blue-green body with white imprint “1002-30” and red to red-orange cap with white imprint “EUR”. Capsule content - white to yellow spherical granules.

Pharmacotherapeutic group: Central muscle relaxant

ATC code: M03BX08

Pharmacological properties

Pharmacodynamics

Cyclobenzaprine cures skeletal muscle spasm not affecting muscle function. Animal studies showed that cyclobenzaprine does not directly affect neuromuscular transmission or directly skeletal muscles. Cyclobenzaprine reduced or eliminated skeletal muscle hypertension on animal models. Data of the studies also showed that cyclobenzaprine primarily affects central nervous system at cerebral trunk level. Inhibition of neuromuscular transmission at the level of spinal cord also plays role in general myorelaxing effect on skeletal muscles. Data available indicate that direct effect of cyclobenzaprine is reduction of tonic somatic motor activity by affecting both gamma (γ)- and alpha (α)-motor systems. Pharmacological studies on animals demonstrated similar effect of cyclobenzaprine and structurally related tricyclic antidepressants, including antagonism in relation to reserpine, potentiation of noradrenaline, express peripheral and central anticholinergic effect and sedation. Cyclobenzaprine induced slight to moderate increase of heart rate in animal studies.

Pharmacokinetics

Absorption

After single administration of cyclobenzaprine in a dose of 15 mg and 30 mg by healthy volunteers (n = 15), dose-dependent increase of C_{max} , AUC_{0-168h} and AUC_{0-∞} has been observed. Maximum cyclobenzaprine concentration in blood plasma is reached in 7 - 8 hours for both dosages.

Cyclobenzaprine pharmacokinetics does not depend on food ingestion. C_{max} value increases to 35%, AUC increases to 20%, however first concentrations of cyclobenzaprine in blood plasma are observed in 1.5 hour, with or without food.

In multiple dose study with administration of 30 mg of cyclobenzaprine once a day within 7 days in a group of healthy volunteers (n = 35) with steady state concentration, 2.5 fold increase of cyclobenzaprine concentration in blood plasma has been observed.

Metabolism and excretion

Cyclobenzaprine to a great degree is metabolized and excreted primarily in the form of glucuronides by urinary way. Cytochrome isoenzymes P-450 3A4, 1A2, and to a lesser degree, 2D6, mediate N-demethylation - one of oxidation ways of cyclobenzaprine metabolism. Elimination half-time of cyclobenzaprine - 32 hours (8- 37 hours range; n = 18); total body clearance - 0.7 L/min after single drug dose administration.

Elderly patients (65 years old and over)

Despite that fact, that no significant difference in C_{max} or T_{max} has been observed, AUC of plasma cyclobenzaprine increased to 40%, cyclobenzaprine elimination half-time was longer in elderly patients at the age of 65 years and more (50 hours) compared to younger patients at the age of 18 -45 years (32 hours). Pharmacokinetics of cyclobenzaprine after multiple dose administration of drug in elderly patients was not evaluated.

Patients with liver function abnormality

In pharmacokinetics study of cyclobenzaprine immediate release in 16 patients with liver dysfunction (15 slight, 1 moderate based on Child – Pugh scores), both AUC, and C_{max} were approximately twice higher compared to values in healthy control group. Pharmacokinetics of cyclobenzaprine in patients with severe liver dysfunction has not been observed.

Indications for use:

Myorix® is indicated as therapeutic appliance for acute pain control in case of muscle spasm, induced by disorders of locomotor system. Drug effect is based on elimination of muscle spasm and its symptoms, i.e. pain syndrome and limited excursion.

Myorix® should be used only during a short period (up to two-three weeks), as long as data on the drug efficiency with longer administration are unavailable, and also due to that fact, that muscle spasm, related to locomotor system disorders usually has short duration and specific treatment for more than three weeks is rarely reasonable.

It was found that Myorix® is not efficient for treatment of muscle spasms induced by disorders of central nervous system, and also with cerebral palsy in children.

Contra indications:

- hypersensitivity to cyclobenzaprine or other drug components;
- children under 18 years;
- coadministration with monoaminooxidase inhibitors (MAO) and administration within 14 days after their withdrawal.
- recent myocardial infarction, fibrillation, AV block or other asequences, congestive heart failure, unstable angina;
- hyperthyroidism.

Administration during pregnancy and breastfeeding

Pregnancy

As long as no controlled studies of cyclobenzaprine use in pregnant women have been performed, it should not be taken during pregnancy.

Lactation

Stop breastfeeding during treatment with cyclobenzaprine, as far as no data of drug permeability to breast milk are available.

Posology and administration

Per os, without chewing, washing down with a small amount of water.

1 capsule of Myorix® in a dose of 15 mg once a day. Some patients might need dose increase up to 30 mg/day. In this case, take 1 capsule of Myorix® in a dose of 30 mg once a day, or 2 capsules of Myorix® in a dose of 15 mg once a day.

It is recommended to take the drug at the same time of a day. Treatment course duration - not more than 2 - 3 weeks.

Adverse reaction

Incidence of side effects of the drug is evaluated as follows:

Very often: $\geq 1/10$,

Often: $>1/100$, $<1/10$;

Not often: $>1/1000$, $<1/100$;

Seldom: $\geq 1/10\ 000$, $< 1/1000$,
Very seldom: $< 1/10\ 000$.

General disorders:

Not often: faintness, sickliness, chest pain, edemas;

Cardiovascular system disorders:

Not often: tachycardia, fibrillation, vasodilation, rapid heartbeat, arterial hypotension/hypertension, myocardial infarction, myocardial conduction defect, stroke;

Disorders of gastrointestinal tract:

Very often: dry mouth;

Often: constipation, nausea, dyspepsia, bad taste;

Not often: vomiting, anorexia, diarrhea, abdominal pain, gastritis, thirst perception, bloat, paraglossa, liver dysfunction;

Seldom: hepatitis, jaundice, cholestasis, paralytic ileus, discoloration of tongue, stomatitis, parotiditis;

Endocrine system disorders:

Not often: syndrome of inappropriate antidiuretic hormone;

Disorders of blood and lymphatic system:

Not often: purpura (hemorrhagic rash), myelosuppression, leukopenia, eosinophilia, thrombocytopenia;

Immune system disorders:

Not often: hypersensitivity response in the form of anaphylactic edema or angioedema, itching, facial edema, urticaria, rash;

Metabolism and nutritional disorders:

Not often: high or low blood glucose level, increased or reduced body weight;

Musculoskeletal system disorders:

Not often: local muscle weakness, myalgia;

Nervous system and mental disorders:

Often: drowsiness, dizziness, increased fatigability, asthenia, blurred vision, headache, nervousness, confused consciousness;

Not often: seizures, coordinatory disturbance, dysarthria, tremor, hypertension, disorientation, insomnia, depressive mood, sensation disorders, anxiety, qualm, psychosis, strange dreams, thought disorder, hallucinations, high excitation, paraesthesia, diplopia, serotonin syndrome, neuroleptic malignant syndrome, high or low libido, gait impairment, delirium, aggressive behavior, paranoia, peripheral neuropathy, Bell's palsy, change of EEG, extrapyramidal disorder;

Respiratory disorders:

Not often: dyspnea;

Disorders of skin and subcutaneous tissue:

Not often: excessive sweating, photosensibilization, alopecia;

Sensory organs disorders:

Not often: change or loss of sense of taste, sonitus;

Disorders of genitourinary system and mammary glands:

Not often: urinary frequency or delay, disturbed urination, urinary tract dilatation, impotency, edema of testicle, gynecomastia, breast augmentation, galactorrhea.

If any side effects from patient information leaflet deteriorate or any other side effects not indicated therein are observed, **call the doctor**.

Overdosage

Overdose symptoms: disturbed consciousness (drowsiness to coma), agitation, nausea, vomiting, ataxia, tremor, low or (slightly) high blood pressure, dizziness, convulsive state, sinus tachycardia or ventricular tachycardia or bradycardia, change of ECG (QT interval elongation, His bundle block, QRS complex dilatation).

Postmarketing experience of administration showed that most often overdosage with cyclobenzaprine was associated with concurrent administration of alcohol and/or other psychotropic medication, there are also several reports about fatal cases.

Based on clinical experience, it is recommended in recipes for cyclobenzaprine to prescribe as low volume of the drug as possible, enough for the next visit of patient, in order to reduce risk of intended overdose.

Treatment: symptomatic and supportive therapy. Specific antidotes are not known. Continuous monitoring of vital functions is recommended (breathing, blood circulation and heart rhythm). Immediate gastric lavage, administration of charcoal to induce drug absorption are recommended in case of overdose. It is not recommended to induce vomiting due to risk of vomit aspiration. Forced diuresis, dialysis, blood transfusion are inefficient.

Drug-to-drug interaction

Due to structural similarity with tricyclic antidepressants, cyclobenzaprine can pose a threat to life when interacting with MAO inhibitors. In patients taking cyclobenzaprine concurrently with MAO inhibitors hyperthermic episodes and seizures have also been observed.

The drug can intensify effect of ethanol, barbiturates and other drug products inhibiting CNS; increase the risk of seizures in patients taking tramadol. The drug can block antihypertensive effect of guanethidine and in the same way acting compounds.

Cases of serotonin syndrome have been reported during coadministration of cyclobenzaprine with other drug products, such as selective serotonin reuptake inhibitors (SSRI), selective serotonin noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants, tramadol, bupropion, trimeperidine, verapamil or MAO inhibitors (ref. to *Special Precautions* Section).

Special precautions

Considering similar pharmacological effect of cyclobenzaprine with other drug products of tricyclic structure, consider probability of withdrawal syndrome with administration of Myorix®, despite that fact that similar cases for this drug have not been registered. Sharp treatment cessation after long period of administration can cause nausea, headache and sickness.

In case of suspected hypersensitivity response (ref. to *Side Effect* Section) stop administration of Myorix®.

Myorix® should be used only during a short period (up to two-three weeks), as long as data on the drug efficiency with longer administration are unavailable, and also due to that fact, that muscle spasm, related to locomotor system disorders usually has short duration and specific treatment for more than three weeks is rarely reasonable.

It was found that Myorix® is not efficient for treatment of muscle spasms induced by disorders of central nervous system or cerebral palsy in children (ref. to *Indications* Section).

Serotonin syndrome

In case of administration of cyclobenzaprine in combination with other drug products (ref. to *Drug-to-drug interaction* Section) there are reports on potentially life threatening serotonin syndrome. Serotonin syndrome symptoms manifest in the form of mental change (e.g., confused consciousness, high excitation, hallucinations), autonomic nervous system instability (e.g., diaphoresis (diaphoresis), tachycardia, unstable arterial pressure, hyperthermia), disturbed

neuromuscular transmission (e.g., tremor, ataxia, hyperreflexia, myoclonus, rigid muscles), gastrointestinal disorders (e.g., nausea, vomiting, diarrhea). In case the above reactions take place, immediately stop treatment with Myorix® and any associated serotonergic medicinal product and start symptomatic treatment. If associated treatment with Myorix® and other serotonergic medicinal products is clinically reasonable, it is recommended to provide thorough monitoring, especially during the beginning of therapy or dose increase.

Effects, similar to effects of tricyclic antidepressants.

Cyclobenzaprine has similar structure with tricyclic antidepressants (amitriptyline, imipramine). There are registered reports that tricyclic antidepressants cause heart rhythm disorder, sinus tachycardia, increased conduction time based on cardiac conduction system, which may lead to myocardial infarction or stroke (ref. to *Contraindications* Section).

Some of more serious reactions of CNS, observed in tricyclic antidepressants, were observed also in studies of cyclobenzaprine use for other indications and usually in doses far exceeding doses recommended for use in case of skeletal muscle spasms. In case of clinically significant symptoms of effect on CNS, consider possibility to withdraw treatment with Myorix®.

Elderly patients

It is not recommended to use Myorix® in elderly patients due to increase of cyclobenzaprine content in plasma to 40 % and increase of elimination half-time to 56 % after administration of the drug by elderly patients compared to younger patients.

Patients with liver function abnormality

It is not recommended to use Myorix® in patients with slight, moderate or severe liver dysfunction due to double increase of cyclobenzaprine content in plasma in patients with slight liver dysfunction compared to patients without liver dysfunction due to limited possibility of drug dose change.

Atropine-like action

Prescribe Myorix® with care to patients with data on urinary retention, angle-closure glaucoma, elevated intraocular pressure in medical history, and in patients taking anticholinergic drugs due to atropine-like action of cyclobenzaprine.

Effects on ability to drive and use machines

Pursuant to adverse reactions profile, it is recommended to abstain from activity, requiring high alertness and promptness of psychomotor reaction, e.g., driving vehicles or working with machines and mechanisms.

Presentation

14 extended release capsules in a blister made of PVC/Al. foil. 1, 2 blisters with Patient Information Leaflet in a cardboard pack.

Storage conditions

Store at a temperature under 25° C.

Keep out of reach of children.

Shelf life

3 years.

Do not use the drug after expiration date.

Dispensing conditions:

On prescription.

Manufacturer/MA Holder:

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Adare Pharmaceuticals S.r.l.,
845 Center Drive, Vandalia, Ohio 45377, USA

Prepacker/Packer/Release quality control:

Personal Protected Data



For customer complaints:

OOO Takeda Pharmaceuticals

Personal Protected Data

