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

SAP Approve Date: 24-May-2017

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- 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.

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Statistical Analysis Plan

Sponsor:	Takeda Pharmaceutical LLC.
Sponsor Protocol Number:	CYC-RR-001
Atlant Clinical Protocol Code:	3502
Study 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.

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History of changes:

Version	Date	Modified by	Description of changes
1.0	24-May-2017	Personal Protected Data	Initial issue

Table of Contents

1. Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
CER	Cyclobenzaprine HCl Extended Release
DBL	Data Base Lock
(e)CRF	Case Report Form (electronic)
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
GEE	Generalized Estimating Equations
hCG	human Chorionic Gonadotropin
HCl	Hydrochloride
HIV	Human Immunodeficiency Virus
HLT	High Level Term
ICD-10	International Classification of Diseases, 10th revision
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LFT	Liver Function Tests
LOCF	Last Observation Carried Forward
M	Mean
MAO	Monoamine Oxidase
Max	Maximum
Med	Median
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
pH	potential of Hydrogen
PP	Per-Protocol
PPS	Per-Protocol analysis Set
PT	Preferred Term
PTE	Pretreatment Event
Q1	First Quartile
Q3	Third Quartile
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software®
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SNRIs	Serotonin Norepinephrine Reuptake Inhibitors

SOC	System Organ Class
SOP	Standard Operating Procedure
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO DD	World Health Organization Drug Dictionary

2. Introduction

According to ICH E9, “a statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data”.
Additionally SAP describes the derived variables and specifies the statistical outputs – tables, figures and listings.

3. Protocol Overview

3.1. Study 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.

3.2. Study Objectives

3.2.1. 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.

Primary Endpoint:

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

3.2.2. Secondary Objective

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

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.

3.2.3. Additional Objectives

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

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
- [redacted]

3.3. 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.

3.4. Randomization and Blinding

The randomization list was generated and stored according to Atlant Clinical SOP. The randomization is applied via IWRS integrated into EDC system.
The investigator or the investigator's designee utilizes the IWRS to randomize the subject into the study. The medication identification (ID) number of the investigational drug then is provided by the IWRS. The investigational drug is dispensed on the Baseline visit.
Randomization takes place on Day1 (could be the same day at which Screening visit is performed).
Study is double-blind. Blinding is applied using IWRS system (IWRS assigns the investigational drug bottle number).
Study data unblinding could be performed after the DBL only.
The investigator shall not break the IP blinding 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 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 eCRF.
If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study. Such subjects will be excluded from PP analysis set.

3.5. Sample Size Estimation

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 ordinally 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.

3.6. Study Population

Screened subjects could be randomized if met all of the inclusion criteria and none of the exclusion criteria.

3.6.1. 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.
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.

3.6.2. 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.

3.6.3. 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 (eCRF) using the following categories.

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 **Error! Reference source not found.**), if the following circumstances occur at any time during study medication treatment:

     - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
     - ALT or AST >5 × ULN and persists for more than 2 weeks, or
     - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
     - ALT or AST >3 × 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 **Error! Reference source not found.**.
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.

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described above. 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.

3.7. Study Assessments

The summary of the study procedures are presented on the table 3.1.

Table 3.1 Schedule of Study Procedures.

	≤5 Day Screening [a]	**Day 1 Randomization** [h]	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 15 Study Termination**[b]	**Follow up**[c]
Clinic Visit		**Visit 1**		**Visit 2**				**Visit 3**								**Visit 4**	**Phone contact**
Visit window				+/- 1 day				+/- 1 day								+1 day	+/- 1 day
Informed Consent	X																
Inclusion/Exclusion Criteria	X																
Demographics and medication history	X																
Medical History, Concurrent medical condition	X																
Vital Signs	X	X		X				X								X	
ECG	X															X	
Physical Examination	X															X	
Weight, Height[g]	X															X	
Pregnancy Test (if applicable)	X															X	
Clinical Laboratory Tests[e]	X															X	
Concomitant Treatments[i]	X	X		X				X								X	
Pre-Treatment/Adverse Events	X	X		X				X								X	X
Study Drug dispense, return and compliance review[f]		X		X				X								X	
Physician Assessments:																	
Presence of Muscle Spasm		X		X				X								X	
Presence of Local Pain		X		X				X								X	
Limitation of Range of Motion		X		X				X								X	
Limitation of Activities of Daily Living		X		X				X								X	
Physician's Clinical Global Assessment[d]				X				X								X	
Subject Assessments:																	

Intensity of Local Pain		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject's Rating of Medication Helpfulness[d]			X	X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]																	
Relief from Local Pain[d]			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		
Restriction in Activities of Daily Living[d]			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		
[redacted]																	
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

3.7.1. Demographic and baseline data

The following demographic and baseline data will be collected at the screening visit:

- Date of birth, sex, race and smoking status;
- Height, Weight;
- Prior/Concomitant treatments;
- Medical history/Concurrent medical conditions.

3.7.2. Efficacy assessments

Physician's assessments will be performed on every visit during the treatment period. Subject's assessments will be performed every day during the treatment period.

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:**

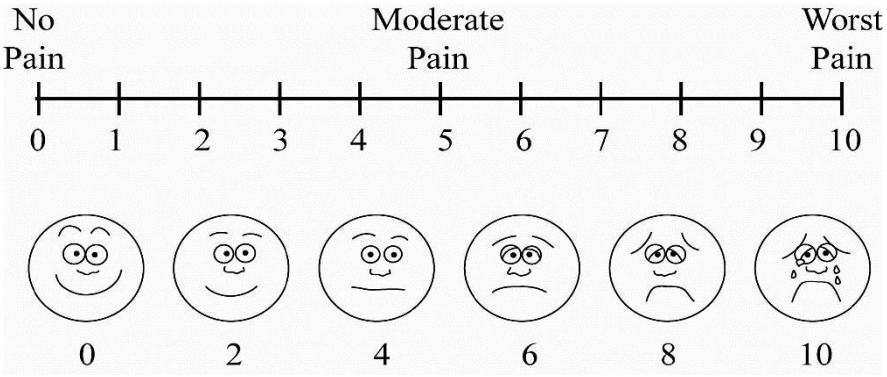
  Subjects will be asked to assess on a daily basis (in the daily diary) the change in the severity of restriction in the activities of daily living compared to Baseline (Visit 1) using the following 5-point rating scale:
  "1 = worsening"
  "2 = no change"
  "3 = mild improvement:"
  "4 = moderate improvement"
  "5 = marked improvement"
  Assessment of the subject's answers will be made for the Day 3, 7 and 15.

- **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.

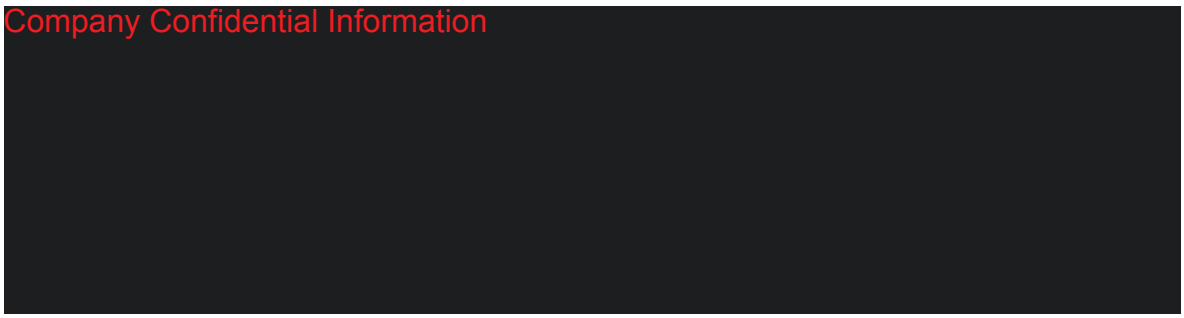
- **Subject-Rated Clinical Global Impression:**

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.

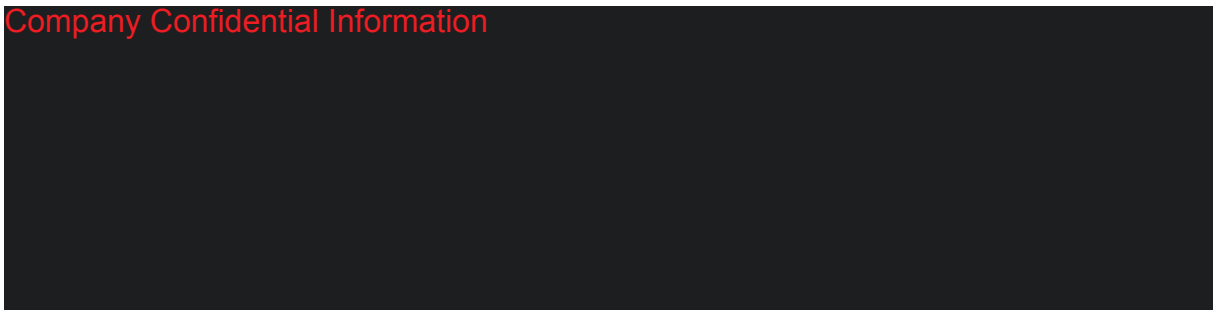
The safety and tolerability assessment in this study will include:

- Company Confidential Information

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

- Company Confidential Information

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

- 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-pointrating 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)

- **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)

3.7.3. Safety assessments

Adverse events:

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. PTEs are assessed at the Screening visit.
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. AEs are assessed during the treatment and follow-up periods.
TEAEs are defined as AEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after study drug administration.
Additional explanations for judging PTEs and AEs (TEAEs) are presented in the Study Protocol, section 10.1.3.
Following information about PTEs and AEs (TEAEs) will be collected:

- Seriousness (with type of SAE) or not
- Severity
- Causality
- Relationship to Study Procedures

- Start Date
- End Date
- Frequency
- Action Concerning Study Medication
- Outcome and date of resolution

Vital Signs:

- Sitting blood pressure (resting more than 5 minutes)
- Pulse (bpm)

Vital signs will be collected at every visit during the treatment period.

Physical Examination:

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.
Physical Examination will be collected at the Screening visit and Visit 4.

Clinical Laboratory Tests:

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

Clinical Laboratory Tests will be collected at the Screening visit and Visit 4.

ECG:

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.
ECG results will be collected at the Screening visit and Visit 4.

3.7.4. Compliance

Compliance data will be collected on Visits 2, 3 and 4.
Treatment compliance for entire treatment period will be calculated at Visit 4 using the formula:
Compliance in % = (# tablets taken during treatment period / # tablets to be taken during treatment period)*100.

3.7.5. 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.

4. Derived Variables and Definitions

- Subjects' AGE will be calculated subtracting Date of the Screening Visit minus Date of Birth (integer).
- Dates will be converted into ISO8601 format.
- Medical history/concurrent medical condition record will be assessed as medical history if it stops before the date of the Screening Visit and such record will be assessed as concurrent medical condition if it doesn't.
- Prior/concomitant medication record will be assessed as prior medication if it stops before the date of the Screening Visit and such record will be assessed as concomitant medication if it doesn't.
- Prior/concomitant medication record will be divide into medications and procedures in SDTM datasets.
- Variables --DY (Study Day) will be derived as (date of interest) minus (TREATMENT VISIT 1 date) plus 1. In integer days.
- Compliance in % = (# tablets taken during treatment period / # tablets to be taken during treatment period)*100.
- Average scores will be calculated as arithmetic mean.

5. Statistical Methodology

5.1. General

All analyses will be performed and presented by treatment group.
Categorical data will be presented using absolute frequencies and percentages. The percentage will not be presented when the absolute frequency is zero. Unless stated otherwise, the denominator for percentage calculations will be the total number of subjects in the applicable analysis set.
Continuous data will be summarized using descriptive statistics, and the following parameters will be reported:

- number of valid observations (n) and missing observations (nmiss);
- arithmetic mean (M) and standard deviation (SD);
- median (Med);
- first (Q1) and third quartiles (Q3);
- minimum (Min) and maximum (Max).

Tests will be two-sided and performed at the 5 % significance level if not otherwise specified. When reporting the outcome of significance tests, the p-value will be reported. Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, or mathematical or scientific rationale. Extreme values will be presented with a number of decimals equal to the appropriate number for that variable; mean values and other descriptive parameters will be presented with one decimal more. Percentages will be presented with one decimal and a percentage sign. P-values will be presented with 4 decimals or as '<.0001'.

Data will be presented in SDTM and ADaM datasets and listings. Mock tables, figures and listings titles are presented in the section 6 of this SAP. Patient data listings will be presented according to the ICH Guideline E3 Structure and Contents of Clinical Study Reports.
All statistical analyses will be performed using SAS® version 9.4 or higher.

5.2. Disposition of subjects

The disposition of subjects will be presented in the table for the numbers of screened subjects, screening failures (in total and by reason), and randomized subjects.

- Screened subject is defined as a subject that has attended the screening visit.
- Screening failure is defined as a subject withdrawn before randomization.
- Randomized subject is defined as a subject that complies with all inclusion and exclusion criteria and got the randomization number in IWRS.

Based on randomized subjects, the number and percentage of the following subjects subsets will be presented:

- Subjects did not take any dose of the study medication.
- Subjects completed the study.
- Subjects prematurely withdrawn from the study in total and by reason.
- Subjects in the safety analysis set, the full analysis set and the per-protocol analysis set.

5.3. Protocol Deviations

List of all Protocol Deviations/Violations (with decisions to exclude subjects from analysis sets) must be finalized before DBL. Protocol Deviations will be presented in a patient data listing.

5.4. 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 analyzed 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 analyzed 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.

5.5. Demographic and Baseline Data

Age, sex, race, smoking status, height, weight and main diagnosis will be presented descriptively for both of the FAS and the PPS.

5.6. Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 and presented in the separate tables by system organ class (SOC) and preferred term (PT). For each SOC and PT, the number and percentage of subjects with a condition in that SOC or PT will be presented descriptively for the safety analysis set.

5.7. Prior and Concomitant Treatment

Medications will be coded using the World Health Organization Drug Dictionary (WHO DD) version Sep 2016. For each therapeutic main group (the second level term in the Anatomical Therapeutic Chemical [ATC] classification system) and preferred name, the number and percentage of subjects will be presented for the safety analysis set. If the preferred name is not available for a medication, the chemical subgroup (ATC level 4) will be displayed instead.

Concomitant procedures will be presented in the descriptive table by the original term. For each original term, the number and percentage of subjects will be presented descriptively for the safety analysis set.

5.8. Efficacy Analysis

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

For all 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 (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.

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

5.8.1. 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 endpoint 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.

Supportive analysis:

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:

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 analyzed 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 assess 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:

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.

5.8.2. 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 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 analyzed 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.

Company Confidential Information

[redacted] Results will be presented in safety section

5.9. Safety Analysis

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

5.9.1. Adverse events

All AEs will be coded by system organ class (SOC), high level term (HLT), and preferred term (PT) as minimum using MedDRA version 20.0. TEAEs will be summarized by treatment group, system organ class (SOC) and preferred term (PT). 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 drug-related TEAEs.

Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

5.9.2. Safety Laboratory Evaluation

Individual results of safety laboratory tests from hematology, chemistry, and urinalysis will be summarized and listed. Results that meet Takeda's markedly abnormal criteria (except urinalysis and test for hCG) will be summarized in the same tables. Baseline, postdose and change from Baseline to postdose laboratory data will be summarized (except test for hCG) All clinical laboratory data will be listed.

5.9.3. 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.

5.9.4. ECGs

Individual ECG results will be summarized by following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. All ECG data will be provided in the data listings.

5.9.5. Physical Examination

All Physical Examination data will be provided in the data listings only.

5.9.6. Exposure

Individual results of the exposure duration will be summarized in table and provided in the data listings.

5.10. Compliance Evaluation

Descriptive statistics table on compliance by Visits 2, 3, 4 will be presented.

5.11. Interim Analysis

No interim analysis is planned.

5.12. Changes to Planned Analysis

- ECG data analysis will not be performed as planned in the Protocol (Section 13.1.4.4) due to Protocol defined ECG assessment assumes to collect the categorical data only. (Section 9.1.12 – *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.*)
- The Protocol consists a potential discrepancy. «Company Confidential Information [redacted] are listed in Other Efficacy Endpoints (Protocol section 13.1.3). At the same time, it may be consider as safety and tolerability assessments according to Protocol section 9.1.6. For clarity, all this data will be analyzed in the efficacy section.

6. Tables, Figures and Listings

Mock tables and figure titles are listed below.

6.1. Disposition of subjects

Table 1. Disposition of subjects

	CER 15 mg	Placebo	Total
Screened			xxx
Screening failures			xxx
Randomized	xx	xx	xxx
Did not take any dose of the study medication	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Prematurely withdrawn	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Completed	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Analysis sets			
Safety analysis set	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Full analysis set	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Per-protocol analysis set	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Percentages are based on the number of randomized subjects.			

Table 2. Screening failures

	Total
Screening failures	xxx
Primary reason	
<reason>	xxx (xx.x%)
<reason>	xxxx (xx.x%)
Percentages are based on the number of screening failures.	

Table 3. Reason for premature withdrawal from the study. Randomized subjects

	CER 15 mg (N=xx)	Placebo (N=xx)	Total (N=xxx)
Prematurely withdrawn	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Primary reason			
<reason>	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
<reason>	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Percentages are based on the number of randomized subjects.			

6.2. Demographics and baseline data

Table 4. Demographics. Full analysis set

Table 5. Demographics. Per-protocol analysis set

	CER 15 mg (N=xx)	Placebo (N=xx)	Total (N=xxx)
Age (years)			xx
n/nmiss	xx/xx	xx/xx	xxx/xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Sex			
Female	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Male	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)

Race			
European	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
<race>	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
<race>	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Smoking status			
Never smoked	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Former smoker	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Current smoker	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Height (cm)			xx
n/nmiss	xx/xx	xx/xx	xxx/xxx
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx.x	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
Weight (kg)			xx
n/nmiss	xx/xx	xx/xx	xxx/xxx
Mean (SD)	xxx.xx (xxx.xx)	xxx.xx (xxx.xx)	xxx.xx (xxx.xx)
Median	xxx.xx	xxx.xx	xxx.xx
Q1, Q3	xxx.xx, xxx.xx	xxx.xx, xxx.xx	xxx.xx, xxx.xx
Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x

n/nmiss – number of subjects with evaluable/missing data, SD – standard deviation, Q1, Q3 – quartiles.
Percentages are based on the number of subjects in the applicable analysis set.

Table 6. Main Diagnosis. Full analysis set

Table 7. Main Diagnosis. Per-protocol analysis set

	CER 15 mg (N=xx)	**Placebo (N=xx)**
Cervicalgia	xx (xx.x%)	xx (xx.x%)
Low back pain	xx (xx.x%)	xx (xx.x%)
Cervicalgia and low back pain	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)

Percentages are based on the number of subjects in the applicable analysis set.

6.3. Medical history and concurrent medical conditions

Table 8. Medical history. Safety analysis set

Table 9. Concurrent medical conditions. Safety analysis set

System organ class/Preferred term	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
<System organ class>	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)
<System organ class>	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)

Medical history is coded according to MedDRA 20.0.
Percentages are based on the number of subjects in the safety analysis set.

6.4. Prior and concomitant treatment

Table 10. Prior treatment. Safety analysis set

Table 11. Concomitant treatment. Safety analysis set

Therapeutic main group/Preferred name	CER 15 mg (N=xx)	Placebo (N=xx)
<Therapeutic main group >	xx (xx.x%)	xx (xx.x%)
<Preferred name>	xx (xx.x%)	xx (xx.x%)
<Preferred name>	xx (xx.x%)	xx (xx.x%)
<Therapeutic main group >	xx (xx.x%)	xx (xx.x%)
<Preferred name>	xx (xx.x%)	xx (xx.x%)
<Preferred name>	xx (xx.x%)	xx (xx.x%)
Medical history is coded according to WHO DD Sep 2016.		
Percentages are based on the number of subjects in the safety analysis set.		

Table 12. Concomitant procedures. Safety analysis set

	CER 15 mg (N=xx)	Placebo (N=xx)
<Procedure>	xx (xx.x%)	xx (xx.x%)
<Procedure>	xx (xx.x%)	xx (xx.x%)
Percentages are based on the number of subjects in the safety analysis set.		

6.5. Efficacy

6.5.1. Primary Efficacy Endpoints

Table 12. Subject's rating of medication helpfulness. Day 3. Full analysis set

Table 13. Subject's rating of medication helpfulness. Day 3. Per-protocol analysis set

Table 14. Subject's rating of medication helpfulness. Day 7. Full analysis set

Table 15. Subject's rating of medication helpfulness. Day 7. Per-protocol analysis set

Table 16. Subject's rating of medication helpfulness. Day 14. Full analysis set

Table 17. Subject's rating of medication helpfulness. Day 14. Per-protocol analysis set

	CER 15 mg (N=xx)	Placebo (N=xx)
Subject's rating of medication helpfulness	xx (xx.x%)	xx (xx.x%)
0 = poor	xx (xx.x%)	xx (xx.x%)
1 = fair	xx (xx.x%)	xx (xx.x%)
2 = good	xx (xx.x%)	xx (xx.x%)
3 = very good	xx (xx.x%)	xx (xx.x%)
4 = excellent	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Subject's rating of medication helpfulness	xx (xx.x%)	xx (xx.x%)
0-2 = poor, fair or good	xx (xx.x%)	xx (xx.x%)
3-4 = very good or excellent	xx (xx.x%)	xx (xx.x%)
p-value**	0.xxxx	
Percentages are based on the number of subjects in the applicable analysis set.		

* The 2-sample Wilcoxon sum rank test was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 0.05 level of significance.
** The continuity-adjusted Chi-square test will be used to compare the number of "responders" between the Placebo and the CER treatment group to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 0.05 level of significance.

Table 18. Subject's rating of medication helpfulness. Trends in the distribution of ratings. Full analysis set

Table 19. Subject's rating of medication helpfulness. Trends in the distribution of ratings. Per-protocol analysis set

Subject's rating of medication helpfulness	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Day 3	xx (xx.x%)	xx (xx.x%)
0 = poor	xx (xx.x%)	xx (xx.x%)
1 = fair	xx (xx.x%)	xx (xx.x%)
2 = good	xx (xx.x%)	xx (xx.x%)
3 = very good	xx (xx.x%)	xx (xx.x%)
4 = excellent	xx (xx.x%)	xx (xx.x%)
Day 7	xx (xx.x%)	xx (xx.x%)
0 = poor	xx (xx.x%)	xx (xx.x%)
1 = fair	xx (xx.x%)	xx (xx.x%)
2 = good	xx (xx.x%)	xx (xx.x%)
3 = very good	xx (xx.x%)	xx (xx.x%)
4 = excellent	xx (xx.x%)	xx (xx.x%)
Day 14	xx (xx.x%)	xx (xx.x%)
0 = poor	xx (xx.x%)	xx (xx.x%)
1 = fair	xx (xx.x%)	xx (xx.x%)
2 = good	xx (xx.x%)	xx (xx.x%)
3 = very good	xx (xx.x%)	xx (xx.x%)
4 = excellent	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	

Percentages are based on the number of subjects in the applicable analysis set.
* Differences between treatments in the distribution of ratings at the 3 visits was analyzed using a weighted least squares model for marginal homogeneity including a parameter for treatment and treatment-by-visit interaction.

Table 20. Subject's rating of medication helpfulness. Repeated measures analysis. Full analysis set

Table 21. Subject's rating of medication helpfulness. Repeated measures analysis. Per-protocol analysis set

Subject's rating of medication helpfulness	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Day 3	xx (xx.x%)	xx (xx.x%)
0-2 = poor, fair or good	xx (xx.x%)	xx (xx.x%)
3-4 = very good or excellent	xx (xx.x%)	xx (xx.x%)
Day 7	xx (xx.x%)	xx (xx.x%)
0-2 = poor, fair or good	xx (xx.x%)	xx (xx.x%)
3-4 = very good or excellent	xx (xx.x%)	xx (xx.x%)
Day 14	xx (xx.x%)	xx (xx.x%)
0-2 = poor, fair or good	xx (xx.x%)	xx (xx.x%)

3-4 = very good or excellent	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	

Percentages are based on the number of subjects in the applicable analysis set.
* Repeated-measures analysis of proportions using Generalized Estimating Equations (GEE) was used for comparisons among treatments of the trend in proportion of responders over time.

Figure 1. Subject's rating of medication helpfulness. Kaplan-Meier curves for time to improvement. Full analysis set

Figure 2. Subject's rating of medication helpfulness. Kaplan-Meier curves for time to improvement. Per-protocol analysis set

6.5.2. Secondary Efficacy Endpoints

Table 22. The subject-rated relief from local pain. Full analysis set

Table 23. The subject-rated restriction in activities of daily living. Full analysis set

Table 24. The subject-rated restriction of movement. Full analysis set

Table 25. The subject-rated clinical global impression. Full analysis set

<Parameter>	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Day 3	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 7	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 14	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	

Percentages are based on the number of subjects in the full analysis set.
* The 2-sample Wilcoxon sum rank test was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 0.05 level of significance..

Figure 3. Subject-rated relief from local pain. Kaplan-Meier curves for time to improvement. Full analysis set

Table 26. The subject-rated intensity of local pain. Full analysis set

Table 27. Company Confidential Information. Full analysis set

Table 28. Company Confidential Information. Full analysis set

<Parameter>	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Day 1	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	

Day 3	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 7	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 14	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	

Percentages are based on the number of subjects in the full analysis set.
* The 2-sample Wilcoxon sum rank test was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 0.05 level of significance..

Table 29. Physician's clinical global assessment. Full analysis set

Physician's clinical global assessment	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Day 3	xx (xx.x%)	xx (xx.x%)
1 = worse	xx (xx.x%)	xx (xx.x%)
2 = no change	xx (xx.x%)	xx (xx.x%)
3 = slight improvement	xx (xx.x%)	xx (xx.x%)
4 = moderate improvement	xx (xx.x%)	xx (xx.x%)
5 = marked improvement	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 7	xx (xx.x%)	xx (xx.x%)
1 = worse	xx (xx.x%)	xx (xx.x%)
2 = no change	xx (xx.x%)	xx (xx.x%)
3 = slight improvement	xx (xx.x%)	xx (xx.x%)
4 = moderate improvement	xx (xx.x%)	xx (xx.x%)
5 = marked improvement	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 15	xx (xx.x%)	xx (xx.x%)
1 = worse	xx (xx.x%)	xx (xx.x%)
2 = no change	xx (xx.x%)	xx (xx.x%)
3 = slight improvement	xx (xx.x%)	xx (xx.x%)
4 = moderate improvement	xx (xx.x%)	xx (xx.x%)
5 = marked improvement	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
p-value**	0.xxxx	

Percentages are based on the number of subjects in the full analysis set.
* The 2-sample Wilcoxon sum rank test was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 0.05 level of significance.
** Differences between treatments in the distribution of ratings at the 3 visits was analyzed using a weighted least squares model for marginal homogeneity including a parameter for treatment and treatment-by-visit interaction.

Table 30. Presence of muscle spasm. Full analysis set

Table 31. Presence of local pain. Full analysis set

Table 32. Limitation of range of motion. Full analysis set

Table 33. Limitation of activities of daily living. Full analysis set

<Parameter>	CER 15 mg (N=xx)	Placebo (N=xx)
Day 1	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 3	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 7	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	
Day 15	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
<response option>	xx (xx.x%)	xx (xx.x%)
p-value*	0.xxxx	

Percentages are based on the number of subjects in the full analysis set.
* The 2-sample Wilcoxon sum rank test was used to test a null hypothesis of no difference between the treatment groups against a two-sided alternative hypothesis at the 0.05 level of significance.

6.6. Safety

6.6.1. Adverse events

Table 34. Overview of adverse events. Safety analysis set

	CER 15 mg (N=xx)		Placebo (N=xx)	
	n (%)	m	n (%)	m
Any pretreatment events	xx (xx.x%)	xx	xx (xx.x%)	xx
Any serious pretreatment events	xx (xx.x%)	xx	xx (xx.x%)	xx
Any treatment-emergent adverse events	xx (xx.x%)	xx	xx (xx.x%)	xx
Any serious treatment-emergent adverse events	xx (xx.x%)	xx	xx (xx.x%)	xx
Any treatment-emergent adverse events leading to withdrawal	xx (xx.x%)	xx	xx (xx.x%)	xx
Relationship of treatment-emergent adverse events	xx (xx.x%)	xx	xx (xx.x%)	xx
Not related	xx (xx.x%)	xx	xx (xx.x%)	xx
Related	xx (xx.x%)	xx	xx (xx.x%)	xx
Severity of treatment-emergent adverse events	xx (xx.x%)	xx	xx (xx.x%)	xx
Mild	xx (xx.x%)	xx	xx (xx.x%)	xx
Moderate	xx (xx.x%)	xx	xx (xx.x%)	xx
Severe	xx (xx.x%)	xx	xx (xx.x%)	xx

n = number of subjects, m = number of events.
Percentages are based on the number of subjects in the safety analysis set.

Table 35. Pretreatment events. Safety analysis set

Table 36. Serious pretreatment events. Safety analysis set

Table 37. Treatment-emergent adverse events. Safety analysis set

Table 38. Serious treatment-emergent adverse events. Safety analysis set

Table 39. Treatment-emergent adverse events related to the study drug. Safety analysis set

Table 40. Treatment-emergent adverse events leading to withdrawal. Safety analysis set

	CER 15 mg (N=xx)		Placebo (N=xx)	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
<System organ class>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx
<System organ class>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx

Adverse events are coded according to MedDRA 20.0.
n = number of subjects, m = number of events.
Percentages are based on the number of subjects in the safety analysis set.

Table 41. Treatment-emergent adverse events by relationship. Safety analysis set, CER 15 mg

Table 42. Treatment-emergent adverse events by relationship. Safety analysis set, Placebo

	Not Related		Related	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**
<System organ class>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx
<System organ class>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx

Adverse events are coded according to MedDRA 20.0.
n = number of subjects, m = number of events.
Percentages are based on the number of subjects in the safety analysis set.

Table 43. Treatment-emergent adverse events by severity. Safety analysis set, CER 15 mg

Table 44. Treatment-emergent adverse events by severity. Safety analysis set, Placebo

	Mild		Moderate		Severe	
System organ class/Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
<System organ class>	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx
<System organ class>	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx
<Preferred term>	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx

Adverse events are coded according to MedDRA 20.0.
n = number of subjects, m = number of events.
Percentages are based on the number of subjects in the safety analysis set.

Table 45. Treatment-emergent adverse events by relationship and severity. Safety analysis set, CER 15 mg

Table 46. Treatment-emergent adverse events by relationship and severity. Safety analysis set, Placebo

	Mild		Moderate		Severe	
System organ class/Preferred term	**NR**	**R**	**NR**	**R**	**NR**	**R**
<System organ class>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<System organ class>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<Preferred term>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Adverse events are coded according to MedDRA 20.0.
Number of subjects for: NR – Not Related, R – Related.
Percentages are based on the number of subjects in the safety analysis set.

6.6.2. Safety Laboratory Evaluation

Table 47. Hematology. Red blood cells. Safety analysis set

Table 48. Hematology. White blood cells. Safety analysis set

Table 49. Hematology. Hemoglobin. Safety analysis set

Table 50. Hematology. Red blood cells. Safety analysis set

Table 51. Serum Chemistry. Alanine aminotransferase. Safety analysis set

Table 52. Serum Chemistry. Albumin. Safety analysis set

Table 53. Serum Chemistry. Alkaline phosphatase. Safety analysis set

Table 54. Serum Chemistry. Aspartate aminotransferase. Safety analysis set

<Parameter (unit)>	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Baseline		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Takeda's markedly abnormal criteria met, n (%)	xx (xx.x%)	xx (xx.x%)
Final visit (Visit 4)		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Takeda's markedly abnormal criteria met, n (%)	xx (xx.x%)	xx (xx.x%)
Change from baseline to final visit		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx

Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x

Percentages are based on the number of subjects in the safety analysis set.
The baseline assessment was performed at the screening visit.

Table 55. Urinalysis. pH. Safety analysis set

pH	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Baseline		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Final visit (Visit 4)		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Change from baseline to final visit		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x

Percentages are based on the number of subjects in the safety analysis set.
The baseline assessment was performed at the screening visit.

Table 56. Urinalysis. Protein. Safety analysis set

Protein (g/L)	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Baseline		
n/nmiss	xx/xx	xx/xx
Mean (SD)	x.xxxx (x.xxxx)	x.xxxx (x.xxxx)
Median	x.xxxx	x.xxxx
Q1, Q3	x.xxxx, x.xxxx	x.xxxx, x.xxxx
Min, Max	x.xxx, x.xxx	x.xxx, x.xxx
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Final visit (Visit 4)		
n/nmiss	xx/xx	xx/xx
Mean (SD)	x.xxxx (x.xxxx)	x.xxxx (x.xxxx)
Median	x.xxxx	x.xxxx
Q1, Q3	x.xxxx, x.xxxx	x.xxxx, x.xxxx
Min, Max	x.xxx, x.xxx	x.xxx, x.xxx
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Change from baseline to final visit		
n/nmiss	xx/xx	xx/xx
Mean (SD)	x.xxxx (x.xxxx)	x.xxxx (x.xxxx)
Median	x.xxxx	x.xxxx
Q1, Q3	x.xxxx, x.xxxx	x.xxxx, x.xxxx
Min, Max	x.xxx, x.xxx	x.xxx, x.xxx

Percentages are based on the number of subjects in the safety analysis set.
The baseline assessment was performed at the screening visit.

6.6.3. Vital Signs

Table 57. Systolic blood pressure. Safety analysis set

Table 58. Diastolic blood pressure. Safety analysis set

Table 59. Pulse rate. Safety analysis set

<Parameter (unit)>	**CER 15 mg (N=xx)**	**Placebo (N=xx)**
Baseline		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx
Takeda's markedly abnormal criteria met, n (%)	xx (xx.x%)	xx (xx.x%)
Visit 2		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx
Takeda's markedly abnormal criteria met, n (%)	xx (xx.x%)	xx (xx.x%)
Change from baseline to visit 2		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx
Visit 3		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx
Takeda's markedly abnormal criteria met, n (%)	xx (xx.x%)	xx (xx.x%)
Change from baseline to visit 3		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx
Final visit (Visit 4)		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx
Takeda's markedly abnormal criteria met, n (%)	xx (xx.x%)	xx (xx.x%)
Change from baseline to final visit		

n/nmiss	xx/xx	xx/xx
Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
Median	xxx.x	xxx.x
Q1, Q3	xxx.x, xxx.x	xxx.x, xxx.x
Min, Max	xxx, xxx	xxx, xxx

Percentages are based on the number of subjects in the safety analysis set.
The baseline assessment was performed at the visit 1.

6.6.4. ECGs

Table 60. ECG assessment. Safety analysis set

	CER 15 mg (N=xx)	**Placebo (N=xx)**
Baseline		
n/nmiss	xx/xx	xx/xx
Within normal limits, n (%)	xx (xx.x%)	xx (xx.x%)
Abnormal but not clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Final visit (Visit 4)		
n/nmiss	xx/xx	xx/xx
Within normal limits, n (%)	xx (xx.x%)	xx (xx.x%)
Abnormal but not clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)
Clinically significant, n (%)	xx (xx.x%)	xx (xx.x%)

Percentages are based on the number of subjects in the safety analysis set.
The baseline assessment was performed at the screening visit.

6.6.5. Exposure

Table 61. Duration of exposure. Safety analysis set

	CER 15 mg (N=xx)	**Placebo (N=xx)**
Duration of exposure (days)		
n/nmiss	xx/xx	xx/xx
Mean (SD)	x.xxxx (x.xxxx)	x.xxxx (x.xxxx)
Median	x.xxxx	x.xxxx
Q1, Q3	x.xxxx, x.xxxx	x.xxxx, x.xxxx
Min, Max	x.xxx, x.xxx	x.xxx, x.xxx

6.7. Compliance

Table 62. Treatment compliance. Safety analysis set

	CER 15 mg (N=xx)	**Placebo (N=xx)**
Compliance (%)		
n/nmiss	xx/xx	xx/xx
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx
Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
Min, Max	xx.xx, xx.xx	xx.xx, xx.xx

Treatment compliance for entire treatment period for each subject is calculated at V4 using the formula: Compliance in % = (# tablets taken during treatment period / # tablets to be taken during treatment period) * 100%.

6.8. Listings

Listing 1. Subject-level data

ATLANT CLINICAL
HONESTY. TRANSPARENCY. EXPERTISE.

7. Sign off Page

Sponsor

Approved by: Personal Protected Data

Signature Date

Atlant Clinical Ltd.

Approved by: Personal Protected Data

Biostatistician: Personal Protected Data