PROTOCOL AMENDMENT

PRODUCT NAME/NUMBER:	MEDI7352
PROTOCOL NUMBER:	D5680C00002
EUDRACT NUMBER:	2018-002523-42
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Randomised, Double-Blind, Placebo-Controlled, Dose-Response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Diabetic Neuropathy
PROTOCOL DATE:	Original Protocol Version 1.0, 24-Jul-2018
AMENDMENT 1 DATE:	Amended Protocol Version 2.0, 29-May-2019
AMENDMENT 2 DATE:	Amended Protocol Version 3.0, 21-Feb-2020
AMENDMENT 3 DATE:	Amended Protocol Version 4.0, 01-Oct-2020 (Not submitted/not implemented at sites)
AMENDMENT 4 DATE:	Amended Protocol Version 5.0, 04-Dec-2020
AMENDMENT 5 DATE:	Amended Protocol Version 5.1, 15-Mar-2021 (Specific to Denmark only)
AMENDMENT 6 DATE:	Amended Protocol Version 6.0, 26-Oct-2021
AMENDMENT 7 DATE:	Amended Protocol Version 7.0, 13-Apr-2022
SPONSORED BY:	AstraZeneca AB 151 85 Sodertalje, Sweden
CONTRACT RESEARCH ORGANIZATION:	Premier Research 3800 Paramount Parkway, Suite 400 Morrisville, NC 27560 USA

1 SPONSOR SIGNATURES

PROTOCOL NUMBER:	D5680C00002
PROTOCOL TITLE:	A Randomised, Double-Blind, Placebo-Controlled, Dose-Response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Diabetic Neuropathy

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this Clinical Study Protocol/Amendment.

PPD

PPD

PPD

Date
(Day Month Year)

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AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified in the Reasons for Amendment and Summary of Amended Sections.

2 PROTOCOL SUMMARY

2.1 Synopsis

PRODUCT NAME/NUMBER	MEDI7352
PROTOCOL NUMBER	D5680C00002
EUDRACT NUMBER	2018-002523-42
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Randomised, Double-Blind, Placebo-Controlled, Dose-Response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Diabetic Neuropathy
INDICATION	Painful Diabetic Neuropathy
OBJECTIVES	Primary: To assess the efficacy of MEDI7352 versus placebo on chronic pain in subjects with painful diabetic neuropathy (PDN) currently taking standard of care medication for their PDN pain. Secondary: • To assess the safety and tolerability of MEDI7352 in subjects with PDN • To assess the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of MEDI7352 in subjects with PDN • To characterise the dose-response relationship of MEDI7352 on chronic pain in subjects with PDN Exploratory: CCI [redacted]
RATIONALE	The study is comprised of 4 stages. The first stage will assess safety of CCI [redacted] in the PDN population. The second stage will compare an expected efficacious dose, CCI [redacted], to placebo. The third stage will compare the highest expected efficacious dose, CCI [redacted] to placebo. The fourth stage will study 3 dose levels of MEDI7352 (CCI [redacted], and CCI [redacted]) versus placebo to enable a thorough characterisation of the efficacy dose-response relationship.
STUDY DESIGN	This is a randomised, double-blind, placebo-controlled study of MEDI7352 in subjects with moderate to severe chronic PDN persistent for 6 months or longer, not adequately controlled by standard of care treatments, caused by type 1 or type 2 diabetes mellitus. The study incorporates a screening period of up to 45 days and a 12-week double-blind treatment period during which MEDI7352 or placebo will be administered intravenously (IV) on 6 occasions, with each dose separated by 14 days. There will be a 6-week follow-up period. There will be 4 stages in the study: in the first stage, subjects will be

	randomly assigned to placebo or the lowest dose (CCI) until at least 10 subjects have been recruited. In the second stage, up to a maximum of 30 subjects will be randomly assigned to placebo or CCI of MEDI7352; prior to commencing the second stage, the safety and tolerability experience following administration of multiple doses of CCI in the Phase 1 study of MEDI7352 will be evaluated. In stage 3 of the study, approximately 67 subjects will be randomly assigned to placebo or CCI of MEDI7352 to ensure that sufficient subjects are evaluable for the pre-planned interim analysis. Prior to commencing the third stage, the safety and tolerability experience following administration of multiple doses of CCI in the Phase 1 study of MEDI7352 will be evaluated. Administrative analyses will also be conducted during the third stage of the study to confirm decision making for stage 4 with respect to the exact sample size and dose allocation ratio. Upon enrolment of approximately 67 subjects in stage 3, approximately 165 eligible subjects will be randomly assigned to treatment with equal allocation across 3 dose levels of MEDI7352 or placebo in stage 4, to ensure that approximately 236 subjects are evaluable for the efficacy analysis of stages 2-4 combined.
PLANNED NUMBER OF SUBJECTS	Approximately 272 eligible subjects will be randomly assigned to double-blind treatment with one of 4 dose levels of MEDI7352 (dependent upon stage of the study) or placebo to ensure that approximately 236 subjects are evaluable for the efficacy analysis of stages 2-4 combined.
STUDY ENTRY CRITERIA	Inclusion criteria: **General** 1. Male, or postmenopausal or surgically sterile female, 18 to 80 years of age (inclusive) on the day of randomisation. Post-menopausal women must have had ≥12 months of spontaneous amenorrhea (with follicle-stimulating hormone [FSH] ≥26 mIU/mL in women ≤60 years; women >60 years do not require a FSH test) and must have had a negative pregnancy test result at screening. Surgically sterile women are defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), bilateral salpingectomy, or bilateral tubal ligation. Women who are surgically sterile must provide suitable medical documentation of the adequacy of the procedure; eg, an operative report or confirmatory ultrasound report. Men who are biologically capable of having children must agree and commit to use an adequate form of contraception (see Appendix B) for the duration of the treatment period and for 3 months after the last administration of study drug. A male subject is considered capable of having children even if his sexual partner is sterile or using contraceptives. 2. Body mass index of ≤42 kg/m^2. 3. Subjects must understand the nature of the study and must provide signed and dated written informed consent prior to the initiation of any study procedures. 4. The subject should be willing and able to understand and participate in all scheduled evaluations and to complete all required tests and procedures including the use of subject diaries, as judged by the investigator. 5. The subject must be considered likely to comply with the study protocol and to have a high probability of completing the study, as judged by the investigator. 6. For subjects participating in the optional genetic research, a separate signed and dated written informed consent must be provided. If a subject declines to participate in the genetic research, this will have no influence on the ability of the subject to participate in the study.

	Diagnostic 7. Chronic PDN persistent for 6 months or longer, not adequately controlled by standard of care treatments. 8. Pain (beginning in the feet and with relatively symmetrical onset for 6 months or greater) due to bilateral peripheral neuropathy caused by either type 1 or type 2 diabetes mellitus, with bilateral decrease or absent reflexes at the ankles, or bilateral decrease of a sensory sign in the distal lower extremities, based on medical history and peripheral neurological examination. [NOTE: for sensory evaluation, the relevant components of the Total Neuropathy Score-Nurse (TNSn) for the lower limb should be undertaken, to include sensory symptom score, pin sensibility score, and vibration sensibility score.] 9. A mean pain intensity score of ≥4, as measured on an 11-point (0-10) NRS by completion of a subject diary for a minimum of 7 days prior to Day 1 (ie, Day -7 to Day -1). At least 5 of 7 days need to be recorded by the subject to obtain a valid baseline value. Pain scores from Day -7 to Day -1 will be centrally reviewed by the study team, and if there is significant variability in the scores during this baseline period of pain evaluation, it will be discussed with the investigator and the subject may be excluded. **Concomitant medication** 10. The subject must be willing and able to discontinue all NSAID or COX-2 analgesic therapy from the start of the washout period until the end of follow-up. This includes over-the-counter (OTC) pain medications and topical analgesics that contain an NSAID or COX-2 inhibitor. The use of NSAIDs (eg, ibuprofen, naproxen) or COX-2 medications (eg, celecoxib) at any time during the study and through to completion of drug washout (5 half-lives) is prohibited and contraindicated. 11. Subjects should currently be taking medication for the treatment of PDN. Subjects should be taking at least one of the first-line medications (consistent with regional or local standard of care guidelines for PDN) belonging to *either* the anticonvulsant class (pregabalin or gabapentin) *or* the antidepressant class (duloxetine, venlafaxine, or amitriptyline), but no more than one medication from a single class. Subjects receiving treatment with opioids alone (as a monotherapy) should be excluded, *unless* the opioids are being prescribed as a second-line treatment for PDN because the first-line therapies were found to be poorly tolerated or not efficacious. For all drug classes, subjects should be established on a stable dosing regimen that is consistent with regional or local standards of accepted prescribing practice for no less than 3 months before the anticipated randomisation date. Subjects should be willing to maintain this dosing regimen for the duration of study participation until the last follow-up visit. Subjects must be willing to use only the protocol-specified rescue medications during the study. 12. If the subject is receiving permitted medications for the treatment of non-excluded medical conditions (eg, antihypertensive medication, cholesterol-lowering treatment, antidiabetic medication), the dose and dosing regimen must be stable for at least 28 days before randomisation and should be expected to remain stable for the duration of study participation until at least the last follow-up visit. Exclusion criteria: **General** 1. Requires current treatment with another biologic therapeutic agent. 2. Previously received any form of anti-nerve growth factor (NGF) or anti-tumor necrosis factor (TNF) therapy.

	3. Participation in another clinical study with an investigational product (IP) or device within 60 days or 5 half-lives prior to screening, whichever is longer. 4. Plasma donation within 28 days of screening or any blood donation or blood loss >500 mL within 2 months of screening. 5. Previous allogeneic bone marrow or stem cell transplant. 6. Received non-leukocyte-depleted whole blood transfusion within 120 days of the genetic research sample collection, if participating in the optional genetic research. 7. Poor venous access such that IV drug delivery would be difficult. 8. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at the study site) and in accordance with local regulations. **Medical history** 9. Presence of other clinically significant neuropathy (eg, hereditary neuropathy, inflammatory neuropathy) or other clinically significant disorder (eg, nerve compression injury) involving abnormal peripheral sensation, with an aetiology that is considered to be distinct from that of PDN, and that is likely to interfere with assessment of peripheral nerve function, as judged by the investigator. 10. History of osteonecrosis, rapidly progressive OA, subchondral insufficiency fractures, neurogenic arthropathy, or analgesia-induced arthropathy. 11. Diagnosis of clinically significant OA currently affecting a major joint in the upper extremity (shoulder, elbow, or wrist) or lower extremity (hip, knee, or ankle) or axial spine; or other degenerative disease affecting any joint in subjects for whom, in the opinion of the investigator, there is an identified risk of osteonecrosis, rapidly progressive OA, subchondral insufficiency fractures, neurogenic arthropathy, or analgesia-induced arthropathy. NOTE: The diagnosis and evaluation of OA should be guided by American College of Rheumatology (ACR)-endorsed criteria, where applicable, and should incorporate radiologic investigation for the assessment of OA severity consistent with the relevant ACR guidance (Altman et al. 1986, Altman et al. 1990, Altman et al. 1991)[35,36,37] at the discretion of the investigator, or otherwise guided by local rheumatologic, orthopaedic, or radiologic expert advice. Where Kellgren and Lawrence grading is used for the radiographic evaluation of major joint OA, grade ≥2 would be considered exclusionary for trial participation. In subjects for whom there is evidence of clinically significant sensory impairment in the distal lower extremity (based on medical history, clinical examination, TNSn, or evidence of sensory nerve conduction impairment available from nerve conduction studies), there is an absolute requirement for bilateral feet and ankle radiographs to be undertaken for the evaluation of OA severity to exclude the possibility of neuropathic arthropathy. All radiologic investigations should be reported locally and the reports should be retained in the patient files as source documentation and made available in the event that subsequent adjudication of rheumatologic adverse events is required. Radiologic images should also be retained and made available in the event that subsequent adjudication of rheumatologic adverse events is required. 12. Chronic pain condition, other than PDN, that is likely to interfere with the evaluation of the subject's PDN pain, as judged by the investigator. 13. Presence of any major psychiatric disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, if, in the opinion of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect pain assessment, or affect the subject's ability to complete the study.

	14. Significant cardiovascular disease, including Class 3 or Class 4 (The Criteria Committee of the New York Heart Association (NYHA) classification standards 1994)[38] congestive heart failure (ejection fraction of <40%) or clinically significant stenosis or occlusion of a carotid or vertebral artery or clinically significant arrhythmias. NOTE: Validated NYHA classification standards: • Class 1: cardiac disease but no symptoms and no limitations in ordinary physical activity (no shortness of breath when walking, climbing stairs) • Class 2: mild symptoms (mild angina or shortness of breath) and slight limitation with ordinary physical activity • Class 3: marked limitation due to symptoms, even during less than ordinary activities such as walking 20 to 100 meters; comfortable only at rest • Class 4: severe limitations and symptoms at rest NOTE: Subjects designated as NYHA functional Class 1 or Class 2 are not necessarily excluded from participation. However, such subjects should have left ventricular ejection fraction measured by echocardiography and documented at baseline. 15. Significant or chronic lung disease, including severe or unstable chronic obstructive pulmonary disease (COPD), or severe or unstable asthma. 16. Known or suspected systemic infection, including HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), or tuberculosis (TB) as judged by the investigator or from screening testing. At screening, a QuantiFERON test will be conducted for TB (Nyendak et al. 2009; Duarte et al. 2012; Cush et al. 2010).[39,40,41] 17. History or evidence of any significant autoimmune disease or disorder, including inflammatory bowel disease, multiple sclerosis, or systemic lupus erythematosus. 18. History of severe allergy/hypersensitivity reactions or history of hypersensitivity to immunisations or immunoglobulins. 19. History of cancer within **5 years** of screening or between screening and randomisation, with the exception of non-metastatic basal cell carcinoma of the skin, carcinoma in situ of the cervix, or non-progressive prostate cancer. 20. Transient ischaemic attack or stroke in the last **3 years**. 21. History of alcohol or recreational drug dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria, within **2 years** of screening, with the exception of nicotine dependence, which is permitted. NOTE: Where there is a documented or suspected history of excessive alcohol usage or recreational drug usage, it is expected that the impact of this with respect to risk be evaluated at screening using the appropriate quantitative or semi-quantitative methodologies according to local standards of accepted medical or psychiatric practice. For example, use of the Fast Alcohol Screening Test (FAST) and Alcohol Use Disorders Identification Test (AUDIT) alcohol screening questions for the initial evaluation of harm and risk associated with excessive alcohol consumption. 22. Within **1 year** of screening or between screening and randomisation, any of the following: myocardial infarction, hospitalisation for unstable angina or arrhythmia, or unexplained syncope. 23. Clinically important infection, including chronic, persistent, or acute infection, within **3 months** of screening or between screening and randomisation.

	24. **Current** serious or unstable clinically important illness, including avascular necrosis, respiratory, cardiovascular, gastrointestinal, endocrinologic (excluding well-controlled type 1 or type 2 diabetes), immunologic, haematologic, neurologic, or other major disease that is likely to deteriorate or affect the subject's safety or ability to complete the study, as judged by the investigator. **Procedural contraindications** 25. Any significant medical or surgical procedure or trauma within **28 days** of Day 1, or planned to be undertaken within the timeframe of the clinical trial, that will likely affect the subject's safety or ability to complete the study, or the scientific integrity of the study data, as judged by the investigator. **Physical and neurological examination, vital signs, ECG, laboratory values, and imaging** 26. Clinically important abnormality in the physical and neurological examination, vital signs, or clinical laboratory test at screening that could affect the subject's safety or ability to complete the study, or the integrity of the clinical trial data, as judged by the investigator. 27. Poorly controlled hypertension (defined as systolic blood pressure [SBP] of >165 mmHg and/or diastolic blood pressure [DBP] of >95 mmHg measured in the clinic) or orthostatic hypotension (defined as a sustained reduction of SBP of at least 20 mmHg and/or a DBP reduction of at least 10 mmHg within 3 minutes of standing from a supine position). *Note:* If the blood pressure (BP) measured in the clinic is out of range, the measurements can be repeated on the same day or at another convenient visit. 28. Prolonged QTcF of >470 msec or family history of long QT syndrome, or shortened QTcF of <360 msec or family history of short QT syndrome, or any clinically significant abnormality in ECG rhythm, conduction, or morphology, including but not limited to: • PR/PQ interval prolongation (PR/PQ >220 ms) • intermittent second or third degree atrioventricular (AV) block (AV block II Mobitz Type I, Wenckebach, while asleep or in deep rest is not exclusionary) • bundle branch block (BBB) or intraventricular conduction delay (IVCD) with QRS duration >120 ms 29. Haemoglobin A_1C greater than 10.0% (>10.0%). 30. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >1.5 × the upper limit of normal (ULN) at screening or between screening and baseline. If the enzyme is >1.5 × ULN, the investigator can either exclude the subject at that time or decide to repeat the test once. If the repeat result is still >1.5 × ULN, the subject must be excluded. 31. Screening creatinine clearance of <60 mL/min as determined by the Cockcroft-Gault formula. 32. Clinically significant abnormal findings in coagulation or haematology laboratory tests, as judged by the investigator. 33. A positive pregnancy test at screening. (If the screening urine pregnancy test is more than 7 days before the first day of treatment, it must be repeated prior to the first dose.) 34. Positive drug screen for drugs of abuse (including but not limited to amphetamine, barbiturate, cannabinoids, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene), **unless** there is a documented medical explanation

	for the positive result other than drugs of abuse (eg, the subject takes opioids under medical supervision for pain and the prescribed opioid dosing regimen is expected to be stable and unchanged for the duration of the study; or where cannabinoids are similarly being taken for documented medical reasons).
TEST PRODUCT	Name: MEDI7352 Dose, route, frequency: Dose levels: CCI [redacted]. Each subject will receive 6 doses, 1 dose every 2 weeks (Days 1, 14, 28, 42, 56, and 70), administered IV over a 60-minute period.
CONTROL PRODUCT	Name: placebo Dose, route, frequency: Same as MEDI7352.
PLANNED STUDY SITES	Approximately 40 study sites in approximately 6 countries.

CRITERIA FOR EVALUATION	Efficacy endpoints:
	• Primary efficacy endpoint: change in the weekly average of the average daily pain scores from the baseline week to Week 12, as measured on an 11-point (0-10) NRS.
	• Secondary efficacy endpoints:
	  • Change in the weekly average of the average daily pain score, as measured on an 11-point (0-10) NRS, from baseline to Weeks 2, 4, 6, 8, and 10 of treatment and the week before the follow-up visit.
	  • Percentage of subjects who have achieved ≥30% and ≥50% reductions in the weekly average of the average daily pain score from baseline during Weeks 4, 8, and 12 of treatment and the week before follow-up.
	  • Change in Galer neuropathic pain scale (NPS) from baseline to Days 28, 56, and 84 of treatment and the follow-up visit.
	  • Change in Daily Sleep Interference Scale (DSIS) from baseline to Days 28, 56, and 84 of treatment and the follow-up visit.
	  • Proportion of subjects who have 'improved', 'much improved', or 'very much improved' relative to baseline on the Patient Global Impression of Change (PGIC) on Days 28, 56, and 84 of treatment and the follow-up visit.
	  • Change in the 36-item Short-Form Health Survey (SF-36) from baseline to Day 84 of treatment.
	  • Usage of rescue medication (yes/no) from baseline to Week 12 of treatment.
	Clinical pharmacology endpoints:
	• Pharmacokinetic endpoints:
	  • maximum concentration (C_{max})
	  • time of C_{max} (t_{max})
	  • area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
	  • area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration (AUC_{0-t})
	  • area under the plasma concentration-time curve for the dosing interval (AUC_{tau}) at steady state

	• C_{max} at steady state • volume of distribution at steady state • $t_{1/2}$ • apparent total body clearance at steady state (CL_{ss}) • Pharmacodynamic endpoints: free and/or total NGF measurements in serum/plasma • Immunogenicity (ADA) assessments • Change in the weekly average of the average daily pain scores from the baseline week to Week 12, as measured on an 11 point (0 to 10) NRS, versus dose CCI  Safety endpoints: • Adverse events (AEs) and serious AEs (SAEs) • Physical and neurological examinations • Neuropathy assessments (TNSn), strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments • Vital signs • 12-lead electrocardiograms (ECGs) • Clinical laboratory testing (haematology, chemistry, coagulation, and urinalysis) • Motor and sensory nerve conduction studies • Concomitant medications and therapies • Injection site reactions and infusion reactions
STATISTICAL METHODS	Analysis Populations: • Screening: all subjects who provide informed consent and/or assent and provide demographic and/or baseline screening assessments, regardless of the subject's randomisation and treatment status in the study. • Safety: The safety population will include all subjects who receive at least 1 dose of double-blind study medication. • Modified intent-to-treat (mITT): The modified intent-to-treat population will be used for all efficacy analyses and will include all randomised subjects who receive at least 1 dose of double-blind study medication and have at least 1 post-baseline NRS assessment. • PK: The PK population will include all subjects for whom a PK sample was obtained and analysed. Subject Characteristics and Disposition: Baseline subject characteristics will be listed and included in summaries as appropriate. Investigational product administration will be

	summarized in terms of each subject's total dose and number of infusions received using descriptive statistics. Efficacy Analyses: All efficacy variables will be summarized descriptively including number of observations, mean, standard deviation (SD), minimum, median, and maximum for continuous variables, and frequency of observations in each category and percentage for categorical variables. Primary and secondary endpoint efficacy data will be tabulated according to the 'Observed Cases' approach. In addition, if there is missing data at a key analysis time-point (Weeks 4, 8, and 12) then results will also be tabulated according to 'Last-Observation-Carried-Forward' (LOCF) and 'Baseline-Observation-Carried-Forward' (BOCF). The main statistical analysis of the primary efficacy endpoint at Week 12 will use the multiple comparison procedure modelling (MCP-Mod) approach on LOCF data, which is a well-established statistical methodology for establishing both the existence of a dose response and modelling the underlying dose-response relationship. In addition, changes from baseline in continuous endpoints will be compared between treatment groups using mixed models repeated measures including terms for pooled site, treatment (as a factor), time point (as a factor), the interaction between treatment and time point, and the baseline value of the variable undergoing analysis. Binary outcomes will be analysed using generalized estimating equations, with the models including the same terms as the mixed models repeated measures. Other non-binary categorical endpoints will be analysed using Cochran-Mantel-Haenszel statistics. These analyses will be conducted on observed cases. Further details of the longitudinal modelling will be included in the statistical analysis plan (SAP). Clinical Pharmacology Analyses: PK: Noncompartmental analysis methods will be used. The PK parameters will be summarized by MEDI7352 dose using descriptive statistics. CCI [redacted] CCI [redacted]. Safety Analyses: Safety and tolerability data will be summarised descriptively, including tables, listings, and graphs, as appropriate.
SAMPLE SIZE DETERMINATION	There is no formal sample size calculation for stage 1; 10 subjects in stage 1 is considered sufficient for the initial assessment of safety. The sample size for stages 2-4 combined was determined by a formal power calculation (see below) and the size of stage 3 was defined to confirm decision making for the stage 4 sample size and dose allocation ratio. This study is powered at greater than 80% to detect a statistically significant (1-sided alpha = 0.025) dose-response relationship when the true Week 12 placebo-corrected change from baseline difference at the CCI [redacted] is 1.25 on the 11-point NRS scale (MEDI7352-placebo treatment) and the true dose-response follows a hyperbolic E_{max} relationship, with the effective dose for 50% of the population (ED50) within the range CCI [redacted] This calculation also assumes: • The true SD is 2.4, which is based on other studies undertaken with pregabalin in PDN • The data from stages 2, 3 and 4 are combined so that the number of subjects evaluable for the dose response analysis is 236. The total number of subjects evaluable for efficacy for the placebo, CCI [redacted] and CCI [redacted] doses is equal to 81, 37, 51 and 67, respectively.

	• The dose-response hypothesis test is multiplicity adjusted in order to control the type 1-error. The above calculations were performed using the following parameters: • Population SD (of change from baseline to week 12) = 2.4 • Placebo effect = 1-point reduction in NRS and 450 µg effect = 2.25 reduction from baseline, ie, delta = 1.25 • Linear contrasts were determined from 5 'candidate dose' response models which are all E_{max} models with decreasing potency/increasing ED50: 7.5, 15, 30, 60, 750 µg/kg. The 5th case is essentially linear in dose. • Power was assessed across 16 alternative true dose response curves, 12 E_{max} with ED50 ranging from 0.375 to 750 µg/kg, 3 logistic and 1 quadratic, all having a Week 12 placebo-corrected change from baseline difference at the CCI of 1.25. The overall withdrawal rate is anticipated to be approximately 10%. However, since the primary analysis will use LOCF for withdrawn subjects, and the SD estimate is taken from studies which also used the LOCF approach, the only additional subjects recruited will be to account for withdrawals in stages 2, 3 and 4 if withdrawal occurs at, or prior to, the Week 2 visit. The number of subjects who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated.
STUDY AND TREATMENT DURATION	The planned sequence and maximum duration of the study periods will be as follows: 1. Screening: 45 days 2. Treatment: 12 weeks 3. Follow-up: 42 days The maximum treatment duration for each subject is approximately 12 weeks. The maximum study duration for each subject is approximately 25 weeks.

2.2 Schedule of Events

Table 2-1: Schedule of Events

	Screening /Baseline (7 to 45 Days)[a]	Double-blind Treatment Period (12 Weeks)									Follow-up (or Early Termination) (6 Weeks)
Study Day / Week	**Day -45 to Day -1[a]**	**Day 1**	**Day 14 Week 2 ±3 days**	**Day 28 Week 4 ±3 days**	**Day 42 Week 6 ±3 days**	**Day 56 Week 8 ±3 days**	**Day 70 Week 10 ±3 days**	**Day 71 V7+24 hr**	**Day 77 V7+7 days ±3 days**	**Day 84 Week 12 ±3 days**	**Week 18 ±7 days**
Clinic Visit (V)	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Height and Weight (BMI)	X										
Demographics and Medical History	X										
Physical and Neurological Examination (C=complete; T=targeted)	C	T	T	T	T	T	T			C	C
12-lead Electrocardiogram (ECG)	X	X[b]		X		X				X	X
Motor and Sensory Nerve Conduction Studies	X										X
Urine Drug Screen and Urine Pregnancy Test	X[a]									X	X
Total Neuropathy Score-Nurse (TNSn)	X	X	X	X	X	X	X			X	X
Strength and Deep Tendon Reflexes[i]	X	X	X	X	X	X	X			X	X
Urinalysis	X	X	X	X	X	X	X			X	X
Vital Signs [c]	X	X	X	X	X	X	X	X	X	X	X
CCI											
Randomisation		X[e]									
Training and Reminders on Rating Pain and Entering Ratings on ePRO System[d]	X	X	X	X	X	X	X			X	
Study Drug Infusion (Dosing)		X	X	X	X	X	X				
Injection Site Assessment		X	X	X	X	X	X			X	X
Daily Pain Diary (NRS) via ePRO	X[d]	X	X	X	X	X	X	X	X	X	X
Daily Sleep Interference Scale (DSIS) via ePRO	X[d]	X	X	X	X	X	X	X	X	X	X
Galer Neuropathic Pain Scale	X			X		X				X	X
Patient Global Impression of Change (PGIC)				X		X				X	X
36-item Short-Form Health Survey (SF-36)	X									X	

	Screening /Baseline (7 to 45 Days)[a]	Double-blind Treatment Period (12 Weeks)									Follow-up (or Early Termination) (6 Weeks)
Study Day / Week	**Day -45 to Day -1[a]**	**Day 1**	**Day 14 Week 2 ±3 days**	**Day 28 Week 4 ±3 days**	**Day 42 Week 6 ±3 days**	**Day 56 Week 8 ±3 days**	**Day 70 Week 10 ±3 days**	**Day 71 V7+24 hr**	**Day 77 V7+7 days ±3 days**	**Day 84 Week 12 ±3 days**	**Week 18 ±7 days**
Clinic Visit (V)	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Blood Collection for:											
Haematology, Chemistry, and Coagulation	X	X	X	X	X	X	X			X	X
Serology (HIV, hepatitis B and C, and tuberculosis)	X										
Pharmacogenetic Sampling (Optional)	X										
Haemoglobin A_1c	X										
Immunogenicity (ADA) Sampling	X		X[f]	X[f]		X[f]	X[f]			X	X
CCI											
Pharmacokinetic Sampling[h]		X[f]	X[f]	X[f]	X[f]	X[f]	X[h]	X[h]	X[h]	X[h]	X[g]
CCI											
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Rescue Medication Use[d]	X[d]	X	X	X	X	X	X	X	X	X	
Concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; BMI = body mass index; C = complete; CCI ; DSIS = Daily Sleep Interference Scale; ECG = electrocardiogram; ePRO = electronic patient-reported outcome system; IP = investigational product; IWRS = interactive web response system; CCI NRS = numeric rating scale; PD = pharmacodynamics; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; SF-36 = 36-item Short-Form Health Survey; T = targeted; TNSn = Total Neuropathy Score-Nurse

a The subject must be screened within 45 days before enrolment in the study and at least 7 days before the first day of treatment to allow for 7 days of baseline pain ratings and sleep monitoring. Screening procedures may be performed at 1 or more visits. If the screening urine pregnancy test is more than 7 days before the first day of treatment, it must be repeated prior to the first dose. Urine drug screen tests will be performed at Screening only.

b On Day 1, 12-lead ECGs (3 replicates) will be performed pre-dose; 60 (±10) minutes after start of IP administration; and 2 and 4 hours (±10 minutes) after start of IP administration.

c Vital signs (heart rate [HR], blood pressure [BP], respiratory rate, and body temperature):
- Screening and Day 1: Supine and orthostatic.
- From Day 14 onwards: Sitting and orthostatic.

CCI [redacted]

e If necessary, the randomisation transaction in IWRS can be performed on Day -1.

CCI [redacted]

CCI [redacted]

i Strength (dorsiflexion) and deep tendon reflexes (knee and ankle) are to be scored at every visit alongside the TNSn assessments.

CCI [redacted]

Table 2-2: Timing of Safety Assessments and Safety Blood Sampling on Day 1

		Time after Start of IP Administration						
Assessment	**Pre-dose**	**0 min**	**15 mins**	**30 mins**	**45 mins**	**60 mins**	**2 hours**	**4 hours**
Administration of IP		←	—	—	—	→		
Injection site assessments and infusion reaction assessments			X	X	X	X	X	X
12-lead ECGs (3 replicates)	X					X	X	X
Supine blood pressure, heart rate	X		X	X	X	X	X	X
Standing (orthostatic) blood pressure, heart rate	X					X	X	X
Body temperature	X					X	X	X
Respiration rate	X		X			X	X	X
Total Neuropathy Score, nurse (TNSn)	X							
Targeted physical and neurological exam	X							
Adverse events	←	—	—	—	—	—	—	→
Safety laboratory tests	X							
Concomitant medication use	←	—	—	—	—	—	—	→

Abbreviations: BP = blood pressure; ECG = electrocardiogram; HR = heart rate; IP = investigational product, mins = minutes; RR = respiratory rate; TNSn = Total Neuropathy Score-Nurse

Note:

- 60-minute orthostatic and supine vital sign assessments (blood pressure, heart rate, respiratory rate, body temperature) should be undertaken within 10 minutes window of completing the infusion. For all other vital signs an acceptable window for measurement is ±5 mins of the specified time-point.
- Standing blood pressure and heart rate (orthostatic vital signs) should be measured after 1 minute (>1 minute, <3 minutes) of adopting the standing position.
- Where multiple assessments are being undertaken at the same time-point, the order of assessments should be (1) 12-lead ECG, (2) Vital signs (supine BP, HR, RR and temperature should be performed before standing vital signs), and (3) Blood sampling.
- Safety laboratory tests taken pre-dose will include haematology, clinical chemistry, coagulation, and urinalysis.
- Strength (dorsiflexion) and deep tendon reflexes (knee and ankle) are to be scored at every visit alongside the Total Neuropathy Score-nurse (TNSn) assessments.
- 12-lead ECGs: 60 (±10) minutes after start of IP administration, 2 hours (±10 minutes) after start of IP administration, and 4 hours (±10 minutes) after start of IP administration.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
AUDIT	Alcohol Use Disorders Identification Test
BOCF	Baseline-Observation-Carried-Forward
BP	blood pressure
CL_{ss}	apparent total body clearance at steady state
C_{max}	maximum plasma concentration
CMP	clinical monitoring plan
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CCI	[redacted]
DBP	diastolic blood pressure
DSIS	Daily Sleep Interference Scale
ECG	electrocardiogram
eCRF	electronic case report form
ED50/ED90	the effective dose for 50%/90% of the population
Emax	the maximum effect of the drug
ePRO	electronic patient-reported outcome (system)

FAST	Fast Alcohol Screening Test
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HR	heart rate
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
LOCF	Last-Observation-Carried-Forward
MAD	multiple ascending dose
MCP-Mod	multiple comparison procedure modelling
mITT	modified intent-to-treat
NCA	noncompartmental analysis
NCS	nerve conduction studies
NGF	nerve growth factor
NPS	neuropathic pain scale
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OA	osteoarthritis
OTC	over-the-counter
PD	pharmacodynamic
PDN	painful diabetic neuropathy
PGIC	Patient Global Impression of Change
CCI [redacted]	
PK	pharmacokinetic
PRN	pro re nata (where necessary)

PR (PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
PT	preferred term
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
CCI	[redacted]
RPOA	rapidly progressive osteoarthritis
RR	the time elapsed between 2 consecutive R waves as measured by electrocardiogram
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SF-36	36-item Short-Form Health Survey
SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
t_{max}	time of C_{max}
TNF	tumor necrosis factor
TNFR2	tumor necrosis factor receptor 2
TNSn	Total Neuropathy Score-Nurse
UADR	unexpected adverse drug reaction
ULN	upper limit of normal

5 INTRODUCTION

5.1 Background and Rationale

The latest estimates show that the number of people with diabetes worldwide has risen from 108 million in 1980 to 422 million in 2014,[1] making it one of the most common chronic diseases. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (WHO).[1] This increase in incidence parallels an increasing trend in ageing and in obesity.

There is considerable morbidity and mortality associated with diabetes, not only because of the primary disease but also because of secondary complications. Diabetic neuropathy is the most common long-term complication of diabetes and is a leading cause of peripheral neuropathy (Dyck et al. 1993).[2] The most common form is a chronic distal symmetric sensorimotor polyneuropathy that predominantly affects the feet and legs. The prevalence of diabetic neuropathy increases with duration of diabetes, from 10% at diagnosis to >50% after 25 years. In a large diabetes patient cohort drawn from 28 community clinics in the US, 75% of the subjects had at least one abnormality on nerve conduction studies (NCS) (Vinik et al. 2006).[3] Approximately 10% to 20% of patients with diabetes have peripheral neuropathic pain (painful diabetic neuropathy; PDN). Around 40% to 50% of those with chronic diabetic neuropathy will have PDN and the majority have features of chronic sensorimotor neuropathy (Veves et al. 2008; Young et al. 1993; Galer et al. 2000; Gordois et al. 2003).[4,5,6,7] One epidemiological study reported tingling, shooting, or burning pain in 34% of over 15,000 diabetic patients surveyed in the community (Abbott et al. 2011).[8] Prevalence of pain was greater in patients with type 2 diabetes than for those with type 1 diabetes (35% vs. 22%), greater in females with diabetes than in males (38% vs. 31%), and showed variability between ethnic groups within the study cohort. PDN is often experienced in terms of a burning, stabbing, pricking or aching sensation that is chronic and difficult to manage; it carries a substantial physical, social, and economic burden. Patients frequently experience anxiety, depression, and sleep disturbance. It is estimated that almost half of these patients do not receive any treatment for pain.

First-line treatments for PDN include tricyclic antidepressants, pregabalin, gabapentin, and duloxetine; other treatments include opioids, topical treatments (lidocaine and capsaicin), and non-pharmacological treatments including transcutaneous electrical nerve stimulation and acupuncture. All of these treatments have limitations, with variable efficacy and responder rates; many carry serious safety concerns and the potential for abuse and dependence. The number needed to treat for at least 50% pain relief for duloxetine (60 to 120 mg/day) is 6 (Sultan et al. 2008)[9]; for gabapentin (>1200 mg/day) it is 5.8, and for pregabalin (300 to 600 mg/day) it is 5.0 (Javed et al. 2015).[10] Thus, despite the poly-pharmacy approach to PDN management, fewer than 20% of patients can be expected to achieve meaningful pain relief with the current treatment paradigms. There is a great medical need for new drugs for the treatment of PDN that have improved and more sustained symptomatic effects and better tolerability.

MEDI7352 is a bispecific fusion protein composed of a single chain variable domain fragment (scFv) that binds nerve growth factor (NGF), linked by CH2 and CH3 domains of a human immunoglobulin 1 to tumor necrosis factor (TNF) receptor 2 (TNFR2). The scFv end of MEDI7352 effectively neutralises NGF, preventing its interaction with both its high- and low-affinity receptors, the tropomyosin-related kinase A receptor and the p75 neurotrophin receptor, respectively. The TNFR2 end of MEDI7352 binds TNF in solution, thereby preventing

its interaction with cell surface TNFR2 and the consequent intracellular signalling and biologic effects. MEDI7352 is thus designed to engage two biological mediators, NGF and TNF, both of which are considered to play an important role in sensitisation of the nervous system and in pain pathophysiology (Pezet and McMahon 2006; Hefti et al. 2006; Petty et al. 1994; Dimitroulas et al. 2017; Leung and Cahill 2010).[11,12,13,14,15] In humans, anti-NGF antibodies demonstrate efficacy in clinical studies of osteoarthritis (OA) and chronic lower back pain (Lane et al. 2010; Katz et al. 2011; Brown et al. 2012, 2013; Kivitz et al. 2013; Schnitzer et al. 2015; Spierings et al. 2013).[16,17,18,19,20,21,22] This clinical efficacy appears to require doses of anti-NGF antibodies that are projected to sequester almost all circulating NGF (Neubert et al. 2013).[23] Such high levels of NGF sequestration have, however, raised concerns with regard to the safety of this therapeutic approach (Holmes 2012; Hochberg et al. 2012; Bannwarth and Kostine 2017).[24,25,26] TNF receptor blockers have a well-established role for disease modification in the management of rheumatoid arthritis and other inflammatory joint diseases in which pain is often an important component of the phenotype (Croft et al. 2013).[27] While anti-TNF therapeutics do not carry a primary indication for the provision of analgesia, there is some evidence to suggest that a selected sub-group of OA patients with a marked inflammatory profile may benefit from this therapy (Dimitroulas et al. 2017),[14] and it is thought that TNF blockers can be at least partially efficacious in the setting of clinical neuropathic pain (Leung and Cahill 2010; Cohen et al. 2012).[15,28]

In preclinical studies, administration of MEDI7352 has been shown to produce a significant antihyperalgesic effect at doses that are believed to sequester <10% of circulating NGF. As such, it is hypothesised that the observed efficacy, which occurs at very low levels of NGF suppression, may result as a function of synergy with respect to the co-sequestration of NGF and TNF. Evidence to support such synergy is based on observations of MEDI7352-mediated analgesia being observed with doses at which the individual components of the protein (anti-NGF or anti-TNF), when dosed separately, are inactive. The observation has been made in animal models of both inflammatory pain and neuropathic pain. While the molecular mechanisms underpinning such efficacy remain to be elucidated, MEDI7352 represents a potentially novel approach to the management of chronic pain that may further help to avoid unwanted effects associated with high levels of NGF suppression.

5.2 Clinical Experience

As of 01 June 2021, it is estimated that approximately 116 subjects have been exposed to MEDI7352 in clinical studies. A first-in-human study of MEDI7352 evaluating safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy in subjects with painful OA of the knee has been completed, and 3 clinical studies with MEDI7352 are ongoing:

- Study D5680C00001, the completed first-in-human study
- Study D5680C00002, the present study described within this protocol
- Study D5680C00003, a Phase IIb, randomised, double-blind, placebo-controlled, dose-response study to evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD of MEDI7352 in subjects with painful OA of the knee
- Study D5680C00004, a Phase I, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and immunogenicity of MEDI7352 in healthy volunteers

5.2.1 Phase I Painful Osteoarthritis of the Knee Study

Completed study D5680C00001 was a clinical evaluation of MEDI7352 for safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy in a first-in-human study in subjects with painful OA of the knee (ClinicalTrials.gov Identifier: NCT02508155).

Single (SAD) and multiple (MAD) ascending doses were evaluated against placebo, with review of blinded safety data from each completed dosage cohort undertaken by a Safety Review Committee before further dose escalation. Study Part 1 (SAD) included a total of 53 male and nonfertile female subjects, aged 36 through 75 years, who received single doses of MEDI7352 or placebo. Overall, 39 subjects received MEDI7352 (33 intravenous [IV] and 6 subcutaneous [SC]), and 14 subjects received placebo (12 IV and 2 SC). The MEDI7352 IV doses studied were CCI CCI and CCI . The SC dose was CCI . Study Part 2 (MAD) included a total of 75 male and nonfertile female subjects, aged 31 through 75 years, who received up to 4 planned IV doses of MEDI7352 or placebo administered 2 weeks apart. Overall, 53 subjects received MEDI7352 (CCI or CCI), and 22 subjects received placebo. An additional subject was enrolled and randomised but not dosed due to poor venous access.

In the SAD phase, 17 of 39 subjects (43.6%) treated with MEDI7352 (across all dose levels) and 9 of 14 subjects (64.3%) treated with placebo had at least one treatment-emergent adverse event (TEAE). Most TEAEs were considered by the investigator to be mild or moderate intensity and not related to investigational product (IP). There were no deaths, serious TEAEs, or discontinuations due to TEAEs.

The most common TEAEs among subjects treated with MEDI7352 in the SAD phase (across all dose levels) were headache (12.8%), back pain (7.7%), and epistaxis (5.1%), with no clear dose-response relationship. Among subjects treated with placebo, the most common TEAEs were headache (28.6%) and oropharyngeal pain (14.3%).

In Study Part 2 (MAD), 44 of 53 subjects (83.0%) treated with MEDI7352 (across all dose levels), and 16 of 22 subjects (72.7%) treated with placebo had at least one TEAE. Most TEAEs were considered by the investigator to be of mild or moderate intensity and not related to IP. There were no deaths. There was 1 reported serious TEAE (pneumonia in a subject treated with MEDI7352), which led to the subject's withdrawal. The pneumonia was considered by the investigator to be severe in intensity and not related to the IP or study procedures, as it was considered a complication of influenza (reported simultaneously by several other family members). Four subjects were withdrawn from the MAD phase of the study due to non-serious TEAEs: viral upper respiratory tract infection; erysipelas; nasopharyngitis and pyrexia; and infusion-related reaction. A higher proportion of subjects treated with MEDI7352 had TEAEs of oral herpes and urinary tract infection (5.7% each) compared with subjects treated with placebo (0%). However, the overall incidence of TEAEs in the SOC of infections and infestations was similar among subjects treated with MEDI7352 and those treated with placebo (39.6% and 36.4%, respectively). The most common TEAEs among subjects treated with MEDI7352 in the MAD phase (across all dose levels) were nasopharyngitis (26.4%), headache (28.3%), back pain (11.3%), and arthralgia and oropharyngeal pain (9.4% each). Among subjects treated with placebo, the most common TEAEs were nasopharyngitis and headache (27.3% each). No infusion-related reactions were reported in the SAD phase of the study. One subject treated with MEDI7352 in the MAD phase had a nonserious infusion-related reaction (dyspnoea, flushing, dizziness), which led to discontinuation as noted above. The TEAE began within 3 minutes of the start of the second IV infusion of MEDI7352 (Day 15); treatment was discontinued, and the event resolved in less than 1 hour.

No cases of rapidly progressive OA (RPOA) or osteonecrosis were reported during the study. There were no discernible differences in the TEAE profiles of subjects with and without ADA in either study phase, suggesting that there were no apparent effects of immunogenicity on safety.No clinically significant changes or dose-related trends for mean changes from baseline or differences between MEDI7352- and placebo-treated subjects in either study phase were observed for other safety parameters, including laboratory safety tests (haematology, coagulation, clinical chemistry and urinalysis), vital signs (blood pressures, temperature, and pulse rate), electrocardiogram (ECG) assessments, physical examinations, or neuropathy assessments (Total Neuropathy Score, nurse).

Please refer to the investigator brochure (IB) for further details.

5.2.2 Current Phase 2 Painful Diabetic Neuropathy Study

Here we present the study protocol to evaluate the analgesic efficacy of MEDI7352 further in a human neuropathic pain condition, by conducting a placebo-controlled trial in subjects with PDN. MEDI7352 or placebo will be administered to subjects as an adjunct to existing therapeutics prescribed for PDN. To enable efficient modelling of the dose-response relationship for MEDI7352 in neuropathic pain, it is planned to evaluate 4 dose levels of MEDI7352 and placebo.

As of 01 June 2021, a total of 41 subjects with PDN have received blinded study treatment (up to 6 planned IV doses, administered every 2 weeks). It is estimated that 21 subjects have received MEDI7352 [CCI redacted]) and 20 subjects have received placebo.

A review of blinded safety data showed that 26 of 41 treated subjects (63.4%) have had at least one reported TEAE as of 01 June 2021. There have been no deaths or serious TEAEs.

Three subjects have discontinued IP due to nonserious adverse events (AEs) as listed below; none of which was considered by the investigator to be related to IP:

- A TEAE of cellulitis of moderate intensity (Stage 1, [CCI redacted] MEDI7352 or placebo)
- A TEAE of infection (symptoms of sore throat, fever, nasopharyngitis, tongue burning, and sweating) of mild intensity (Stage 2, [CCI redacted] MEDI7352 or placebo)
- An AE of alanine aminotransferase (ALT) increased of mild intensity that was reported in Stage 2 before the treatment period began and thought to be due to excessive alcohol consumption, and which led to the subject's withdrawal after 3 of 6 planned infusions of IP ([CCI redacted] MEDI7352 or placebo).

Headache was the most commonly reported TEAE overall: 7 of 41 subjects (17.1%), including 3 of 10 subjects (30.0%) in the completed Stage 1 ([CCI redacted] MEDI7352 or placebo), 3 of 26 subjects (11.5%) in the completed Stage 2 ([CCI redacted] MEDI7352 or placebo) and 1 of 5 subjects (20%) in the ongoing Stage 3 (MEDI7352 [CCI redacted] or placebo). All TEAEs reported in each study stage were considered by the investigator to be of mild or moderate intensity.

No clinically significant changes or trends for changes from baseline have been observed for other safety parameters, including ECG assessments; vital signs; laboratory safety tests; and Total Neuropathy Score-Nurse (TNSn) or for parameters measured during motor and sensory NCS.

5.2.3 Phase 2b Painful Osteoarthritis of the Knee Study

In the ongoing Phase IIb study D5680C00003, one subject had received blinded SC study treatment (MEDI7352 [CCI redacted] and [CCI redacted] or placebo) as of 01 June 2021. This subject had

nonserious TEAEs of diarrhoea and irritability, both considered by the investigator to be of moderate intensity. The subject withdrew from the study (ie, consent withdrawal) after receiving 5 of 6 planned SC injections of study treatment.

5.2.4 Phase I Study in Healthy Volunteers

In the Phase I study D5680C00004, 5 subjects had received blinded SC study treatment (MEDI7352 CCI or placebo) as of 01 June 2021. Two of the of 5 treated subjects (40.0%) have had a total of 4 TEAEs as follows (1 subject each): dyspepsia, catheter site erythema, injection site pain, and paraesthesia. All reported TEAEs were considered by the investigator to be of mild intensity. There have been no deaths, treatment-emergent SAEs, or withdrawals due to AEs.

5.3 Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects with PDN may experience a reduction in symptoms as a result of treatment with MEDI7352. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to MEDI7352, as well as those related to medical procedures, including venepuncture undertaken for blood sampling and administration of investigational product (IP). Although no important risks have been identified for MEDI7352 to date in the completed Phase 1 clinical study or the 3 ongoing studies, MEDI7352 may have risks similar to those reported with both anti-NGF and anti-TNF therapies, as well as those reported with therapeutic proteins in general.

Potential risks associated with MEDI7352 include:

- Potential risks based on class effects and mechanisms of action
    - Risks associated with the anti-NGF mechanism
        - Rapidly progressive OA and other joint safety events. This risk is not limited to osteoarthritic joints
        - Sensory abnormalities and peripheral neuropathy
        - Autonomic neuropathy and sympathetic dysfunction
    - Risks associated with the anti-TNF mechanism
        - Increased risk of infection, including tuberculosis, bacterial sepsis, and invasive fungal infections
        - Warnings and precautions for etanercept (anti-TNFα therapy) include hypersensitivity reactions; exacerbation or new onset of demyelinating disease; malignancies, including lymphoma, leukaemia, melanoma and non-melanoma skin cancer; serious haematological reactions including pancytopenia, or aplastic anaemia; new onset or worsening congestive heart failure; reactivation of hepatitis B; autoimmune conditions including autoimmune hepatitis, autoimmune renal disease and a lupus-like syndrome (ENBREL Prescribing Information, ENBREL Summary of Product Characteristics).

- General risks associated with protein therapeutics include immunological reactions: hypersensitivity reactions, injection site reactions, and the consequences of immunogenicity (eg, immune-complex disease).

The most significant adverse effect of anti-NGF monoclonal antibodies has been infrequent clinical cases of RPOA (type 1 and 2) observed in large-scale clinical studies, which led the Food and Drug Administration (FDA) to impose a clinical hold on this mechanism in 2010. At a 2012 Arthritis Advisory Committee meeting that reviewed results of the tanezumab, fulranumab, and fasinumab programs, sponsors presented data showing that these events increased with increased doses of anti-NGFs and particularly when the drugs were dosed concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs).[29]

At the FDA Advisory Committee Meeting in 2021, safety data from 3 studies of tanezumab were presented using a composite joint safety event endpoint to capture events including RPOA type 1, RPOA type 2, osteonecrosis, subchondral insufficiency fracture, and pathological fracture.[30] There was a significantly higher incidence of events in subjects treated with tanezumab (3.2% and 6.2% of subjects treated with tanezumab 2.5 mg and 5 mg, respectively) compared to NSAIDs (1.5% of subjects) or placebo (0% of subjects).[31] In addition, a greater proportion of subjects treated with tanezumab (5.5% and 7.8% of subjects treated with tanezumab 2.5 mg and 5 mg, respectively) required total joint replacements when compared to those treated with NSAIDs (2.6% of subjects) or placebo (4.5% of subjects). [30, 31] Overall, approximately 85% of the total joint replacements occurred in joints KL grade ≥ 3 at baseline;[31] however, some joint safety events including total joint replacement occurred in joints KL grade 0 or 1 at baseline. [30, 31]

It was also notable in the tanezumab programme that composite joint safety events are not limited to arthritis joints. For subjects with joints KL grade 0 or 1 enrolled in the tanezumab study 1058, there was a higher incidence of CJSE in the tanezumab 5 mg treatment arm (19 events, 1.9%) than in the NSAID arm (2 events, 0.2%).[32]

There have been no reports of RPOA or destructive arthropathy in the MEDI7352 clinical program to date.

Peripheral neuropathy—both autonomic and sensory—has also been identified as a risk with anti-NGF antibodies (Bélanger et al. 2018; Dewanjee et al. 2018).[33,34] In the MEDI7352 13-week good laboratory practice toxicology study undertaken in rats, axonal degeneration has been observed in peripheral nerves. No clear dose-response relationship has been observed for this effect, although a trend for increased 'average' severity with increasing dose was noted. It is unclear whether sensory nerves or motor nerves or both are affected. No functional consequences have been observed in neurobehavioural assessments in the animals and the effect has been described as non-adverse in the rodents. The underlying mechanism and potential relevance of the finding to humans is unknown. It is not known whether MEDI7352 might worsen a pre-existing neuropathy as a function of NGF inhibition. For the present clinical study, the risk will be managed through appropriate peripheral nervous system monitoring and will include nerve conduction studies (NCS).

TNF-alpha inhibitors carry labelled safety warnings and precautions regarding the risk of serious infections (including tuberculosis [TB], bacterial sepsis, invasive fungal infections, and other opportunistic infections) and malignancies (including lymphoma and other malignancies). Additional warnings and precautions for etanercept include exacerbation or new onset of

demyelinating disease, lymphoma, pancytopenia or aplastic anaemia, new onset or worsening congestive heart failure, and reactivation of hepatitis B virus (HBV).

General risks of biologic therapies include infusion-related reactions (defined as a collection of signs and symptoms ranging from local skin reactions at the injection site, pyrexia, and an influenza-like syndrome, to an acute anaphylaxis, usually occurring within 2 hours of the infusion; hypersensitivity reactions; and development of anti-drug antibodies to MEDI7352. Antidrug antibodies to MEDI7352 could result in immune-complex disease (with manifestations including arthralgia, serum-sickness, and vasculitis), auto-immunity, or altered MEDI7352 levels or activity.

A summary of the pharmacological properties and known potential risks of MEDI7352 is provided in the current version of the IB. The investigator must become familiar with all sections of the MEDI7352 IB before the start of the study.

6 OBJECTIVES

6.1 Primary Objective

The primary objective is to assess the efficacy of MEDI7352 versus placebo on chronic pain in subjects with PDN currently taking standard of care medication for their PDN pain.

6.2 Secondary Objectives

- To assess the safety and tolerability of MEDI7352 in subjects with PDN
- To assess the PK, PD, and immunogenicity of MEDI7352 in subjects with PDN
- To characterise the dose-response relationship of MEDI7352 on chronic pain in subjects with PDN

6.3 Exploratory Objectives

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Objectives	Endpoints
Primary	
• To assess the efficacy of MEDI7352 versus placebo on chronic pain in subjects with PDN currently taking standard of care medication for their PDN pain	Primary: • Change in the weekly average of the average daily pain scores from the baseline week to Week 12 of MEDI7352 compared to placebo, as measured on an 11-point (0-10) NRS. Secondary: • Change in the weekly average of the average daily pain score, as measured on an 11-point (0-10) NRS, from baseline to Weeks 2, 4, 6, 8, and 10 of treatment and the week before the follow-up visit. • Percentage of subjects who have achieved ≥30% and ≥50% reductions in the weekly average of the average daily pain score from baseline during Weeks 4, 8, and 12 of treatment and the week before follow-up. • Change in Galer Neuropathic Pain Scale (NPS) from baseline to Days 28, 56, and 84 of treatment and the follow-up visit. • Change in Daily Sleep Interference Scale (DSIS) from baseline to Days 28, 56, and 84 of treatment and the follow-up visit. • Proportion of subjects who have 'improved', 'much improved', or 'very much improved' relative to baseline on the Patient

	Global Impression of Change (PGIC) on Days 28, 56, and 84 of treatment and the follow-up visit. • Change in the 36-item Short-Form Health Survey (SF-36) from baseline to Day 84 of treatment. • Change in the amount of rescue medication used (in terms of dosage/day) from baseline to Week 12 of treatment.
Secondary	
• To assess the safety and tolerability of MEDI7352 in subjects with PDN	• Safety and tolerability assessments: AEs and SAEs, physical and neurological examinations, neuropathy assessments (TNSn), strength (dorsiflexion) and deep tendon reflex (knee and ankle) assessments, vital signs, 12-lead ECGs, clinical laboratory testing (haematology, clinical chemistry, coagulation, and urinalysis), motor and sensory nerve conduction, concomitant medication assessment, injection site reaction assessment, and infusion reaction assessments.
• To assess the PK, PD, and immunogenicity of MEDI7352 in subjects with PDN	• Primary PK parameters of MEDI7352 will include maximum concentration (C_{max}), time of C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration (AUC_{0-t}), area under the plasma concentration-time curve for the dosing interval (AUC_{tau}) at steady state, C_{max} at steady state, volume of distribution at steady state, $t_{1/2}$, and apparent total body clearance at steady state (CL_{ss}). • Pharmacodynamics: free and/or total NGF measurements in serum/plasma. • Immunogenicity (ADA) assessments.
• To characterise the dose-response relationship of MEDI7352 on chronic pain in subjects with PDN	• Change in the weekly average of the average daily pain scores from the baseline week to Week 12, as measured on an 11-point (0-10) NRS, versus dose.
Exploratory	
CCI	

7 STUDY DESIGN

7.1 Overall Study Design and Plan

This is a randomised, double-blind, placebo-controlled study of MEDI7352 in subjects with moderate to severe PDN. The study incorporates a screening period of up to 45 days and a 12-week double-blind treatment period during which MEDI7352 or placebo will be administered IV on 6 occasions, with each dose separated by 14 days. There will be a 6-week follow-up period.

Subjects must have chronic PDN persistent for 6 months or longer, not adequately controlled by standard of care treatments, caused by type 1 or type 2 diabetes mellitus. Subjects must have bilateral decrease or absent reflexes at the ankles, or bilateral decrease of a sensory sign in the distal lower extremities, based on medical history and physical or neurological examination.

NSAIDs and COX-2 inhibitors are strictly contraindicated throughout the study. If eligible subjects are using NSAIDs or COX-2 inhibitors at the time of screening, they must be willing to withdraw from them.

Subjects will be required to report pain scores on an 11-point (0-10) numeric rating scale (NRS) by completion of a subject diary for a minimum of 7 days prior to Day 1 (ie, Day -7 to Day -1). If the diary is started prior to Day -7, then data from Day -7 to Day -1 will be used to determine eligibility. At least 5 of 7 days need to be recorded by the subject to obtain a valid baseline value. To be eligible for randomisation, a mean pain intensity score of ≥4 is required. There will be 4 stages in the study: in the first stage, subjects will be randomly assigned to placebo or the lowest dose (CCI) until at least 10 subjects have been recruited. In the second stage, up to a maximum of 30 subjects will be randomly assigned to placebo or CCI of MEDI7352; prior to commencing the second stage, the safety and tolerability experience following administration of multiple doses of CCI in the Phase 1 study of MEDI7352 will be evaluated. In stage 3 of the study, approximately 67 subjects will be randomly assigned to placebo or CCI of MEDI7352. The third stage will include an interim analysis to assess key assumptions of the sample size calculation. Upon enrolment of approximately 67 subjects in stage 3, approximately 165 eligible subjects will be randomly assigned to treatment with equal allocation across 3 dose levels of MEDI7352 or placebo to ensure approximately 236 subjects are evaluable for the efficacy analysis of stages 2 to 4 combined. In summary, the numbers of subjects randomised to receive treatment in the various stages is as follows: at least 10 subjects in stage 1, up to a maximum of 30 subjects in stage 2, an estimated 67 subjects in stage 3, and an estimated 165 subjects in stage 4 (ie, 272 in total across all study stages 1 to 4).

All treatments and assessments will be undertaken in a double-blind fashion. Treatments will be administered IV over a 60-minute period. Subjects will be dosed as outpatients and will participate in 6 independent dosing sessions, once every 2 weeks. Safety and efficacy assessments will be undertaken at each of the dosing sessions and during follow-up visits.

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Efficacy will be evaluated by subject assessments of daily average pain, as measured on an 11-point (0-10) NRS; the Galer Neuropathic Pain Scale (NPS); the Daily Sleep Interference Scale (DSIS); the Patient Global Impression of Change (PGIC); and the 36-item Short-Form Health Survey (SF-36).

The PK, PD (free and/or total plasma/serum NGF) and immunogenicity of MEDI7352 will be characterized.

CCI [redacted].

CCI [redacted].

Safety will be assessed by evaluating adverse events (AEs), clinical laboratory test results, vital sign measurements, and 12-lead ECGs. Physical and neurological examinations will be undertaken. Additional monitoring of the peripheral nervous system will be undertaken through evaluation of TNSn, strength (dorsiflexion), deep tendon reflexes (knee and ankle), and NCS of motor and sensory nerves. Monitoring will be undertaken for injection site reactions and infusion-related reactions. Concomitant medication use will be monitored.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent and/or assent through the posttreatment visits) will be documented.

Medical monitors will review safety data on an ongoing basis. An interim review of blinded aggregate safety data will be undertaken following completion of follow-up for approximately every 30 subjects enrolled in the study (see Section 9.3.1). The interim review will be performed by AstraZeneca Neuroscience in conjunction with the pharmacovigilance and safety agent, MMS Holdings.

Figure 7-1: Study Design

CCI

7.2 Rationale and Discussion of Study Design

A randomised, double-blind, placebo-controlled study design with multiple dose levels of MEDI7352 is appropriate to assess the efficacy, safety, tolerability, PK, PD, and immunogenicity of MEDI7352 as compared to placebo. Subjects must have chronic PDN that is not adequately controlled by standard of care treatments, and will receive MEDI7352 as adjunctive therapy for 12 weeks. Placebo is included in the study to permit comparative assessment of the safety, tolerability, PK, PD, and immunogenicity of MEDI7352, and to further evaluate the balance of benefit and risk of MEDI7352. The study is comprised of 4 stages. The first stage will assess safety of CCI in the PDN population. The second stage will compare an expected efficacious dose, CCI , to placebo. The third stage will compare the highest expected efficacious dose, CCI to placebo and includes an interim analysis that will confirm decision making for stage 4 with respect to exact sample size and dose allocation ratio. If there are no changes following the interim analysis, the fourth stage will study 3 doses of MEDI7352 (CCI) versus placebo to enable a robust characterisation of the efficacy dose-response relationship.

7.3 Selection of Doses in the Study

MEDI7352 has undergone clinical evaluation for safety, PK, PD, and efficacy in a first-in-human study in subjects with painful OA of the knee (ClinicalTrials.gov Identifier: NCT02508155). In that study, testing of single IV doses of up to CCI and repeat ascending IV doses of CCI CCI and CCI every 2 weeks have been completed. Single SC doses of CCI have also been evaluated. No safety or tolerability concerns were reported. A full description of the current clinical experience with MEDI7352 is in Section 5.2.

Based on the results of the first-in-human study, the planned dosages in this protocol are CCI CCI and CCI administered every 2 weeks with a total of 6 doses per subject. Thus, the dose range to be explored in this study encompasses an equivalent dose range that has been studied in the preceding Phase 1 study and the highest dose planned for the current study is the same as the highest dose assessed in the Phase 1 study.

7.4 Study Sites

The study will take place at approximately 40 sites in approximately 6 countries. Each site is anticipated to screen a sufficient number of subjects to randomise approximately 8 subjects. A study site with a high recruitment rate may be allowed to recruit more subjects if other sites have slow enrolment.

7.5 Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the subject information and informed consent form (ICF).

7.6 End of Study Definition

The clinical trial is considered completed when the last subject's last study visit has occurred.

8 SUBJECT POPULATION

8.1 Selection of Study Population and Diagnosis

Approximately 272 eligible subjects will be randomly assigned to double-blind treatment with 1 of 4 dose levels of MEDI7352 (CCI and CCI dependent upon the stage of the study) or placebo to ensure that approximately 236 subjects are eligible for the efficacy analysis of stages 2, 3 and 4 combined.

Subjects who do not meet all of the eligibility criteria will not be enrolled.

8.2 Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

General

1. Male, or postmenopausal or surgically sterile female, 18 to 80 years of age (inclusive) on the day of randomisation. Post-menopausal women must have had ≥12 months of spontaneous amenorrhea (with follicle-stimulating hormone [FSH] ≥26 mIU/mL in women ≤60 years; women >60 years do not require a FSH test) and must have had a negative pregnancy test result at screening. Surgically sterile women are defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), bilateral salpingectomy, or bilateral tubal ligation. Women who are surgically sterile must provide suitable medical documentation of the adequacy of the procedure; eg, an operative report or confirmatory ultrasound report. Men who are biologically capable of having children must agree and commit to use an adequate form of contraception (see Appendix B) for the duration of the treatment period and for 3 months after the last administration of study drug. A male subject is considered capable of having children even if his sexual partner is sterile or using contraceptives.
2. Body mass index of ≤42 kg/m^2.
3. Subjects must understand the nature of the study and must provide signed and dated written informed consent prior to the initiation of any study procedures.
4. The subject should be willing and able to understand and participate in all scheduled evaluations and to complete all required tests and procedures including the use of subject diaries, as judged by the investigator.
5. The subject must be considered likely to comply with the study protocol and to have a high probability of completing the study, as judged by the investigator.
6. For subjects participating in the optional genetic research, a separate signed and dated written informed consent must be provided. If a subject declines to participate in the genetic research, this will have no influence on the ability of the subject to participate in the study.

Diagnostic

7. Chronic PDN persistent for 6 months or longer, not adequately controlled by standard of care treatments.
8. Pain (beginning in the feet and with relatively symmetrical onset for 6 months or greater) due to bilateral peripheral neuropathy caused by either type 1 or type 2 diabetes mellitus, with

bilateral decrease or absent reflexes at the ankles, or bilateral decrease of a sensory sign in the distal lower extremities, based on medical history and peripheral neurological examination. [NOTE: for sensory evaluation, the relevant components of the TNSn for the lower limb should be undertaken, to include sensory symptom score, pin sensibility score, and vibration sensibility score.]

9. A mean pain intensity score of ≥4, as measured on an 11-point (0 to 10) NRS by completion of a subject diary for a minimum of 7 days prior to Day 1 (ie, Day -7 to Day -1). At least 5 of 7 days need to be recorded by the subject to obtain a valid baseline value. Pain scores from Day -7 to Day -1 will be centrally reviewed by the study team, and if there is significant variability in the scores during this baseline period of pain evaluation, it will be discussed with the investigator and the subject may be excluded.

Concomitant medication

10. The subject must be willing and able to discontinue all NSAID or COX-2 analgesic therapy from the start of the washout period until the end of follow-up. This includes over-the-counter (OTC) pain medications and topical analgesics that contain an NSAID or COX-2 inhibitor. The use of NSAIDs (eg, ibuprofen, naproxen) or COX-2 medications (eg, celecoxib) at any time during the study and through to completion of drug washout (5 half-lives) is prohibited and contraindicated.
11. Subjects should currently be taking medication for the treatment of PDN. Subjects should be taking at least one of the first-line medications (consistent with regional or local standard of care guidelines for PDN) belonging to *either* the anticonvulsant class (pregabalin or gabapentin) *or* the antidepressant class (duloxetine, venlafaxine, or amitriptyline), but no more than one medication from a single class. Subjects receiving treatment with opioids alone (as a monotherapy) should be excluded, *unless* the opioids are being prescribed as a second-line treatment for PDN because the first-line therapies were found to be poorly tolerated or not efficacious. For all drug classes, subjects should be established on a stable dosing regimen that is consistent with regional or local standards of accepted prescribing practice for no less than 3 months before the anticipated randomisation date. Subjects should be willing to maintain this dosing regimen for the duration of study participation until the last follow-up visit. Subjects must be willing to use only the protocol-specified rescue medications during the study.
12. If the subject is receiving permitted medications for the treatment of non-excluded medical conditions (eg, antihypertensive medication, cholesterol-lowering treatment, antidiabetic medication), the dose and dosing regimen must be stable for at least 28 days before randomisation and should be expected to remain stable for the duration of study participation until at least the last follow-up visit.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

General

1. Requires current treatment with another biologic therapeutic agent.
2. Previously received any form of anti-NGF or anti-TNF therapy.

3. Participation in another clinical study with an IP or device within 60 days or 5 half-lives prior to screening, whichever is longer.
4. Plasma donation within 28 days of screening or any blood donation or blood loss >500 mL within 2 months of screening.
5. Previous allogeneic bone marrow or stem cell transplant.
6. Received non-leukocyte-depleted whole blood transfusion within 120 days of the genetic research sample collection, if participating in the optional genetic research.
7. Poor venous access such that IV drug delivery would be difficult.
8. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at the study site) and in accordance with local regulations.

Medical history

9. Presence of other clinically significant neuropathy (eg, hereditary neuropathy, inflammatory neuropathy) or other clinically significant disorder (eg, nerve compression injury) involving abnormal peripheral sensation, with an aetiology that is considered to be distinct from that of PDN, and that is likely to interfere with assessment of peripheral nerve function, as judged by the investigator.
10. History of osteonecrosis, rapidly progressive OA, subchondral insufficiency fractures, neurogenic arthropathy, or analgesia-induced arthropathy.
11. Diagnosis of clinically significant OA currently affecting a major joint in the upper extremity (shoulder, elbow, or wrist) or lower extremity (hip, knee, or ankle) or axial spine; or other degenerative disease affecting any joint in subjects for whom, in the opinion of the investigator, there is an identified risk of osteonecrosis, rapidly progressive OA, subchondral insufficiency fractures, neurogenic arthropathy, or analgesia-induced arthropathy.

    NOTE: The diagnosis and evaluation of OA should be guided by American College of Rheumatology (ACR)-endorsed criteria, where applicable, and should incorporate radiologic investigation for the assessment of OA severity consistent with the relevant ACR guidance (Altman et al. 1986, Altman et al. 1990, Altman et al. 1991)[35,36,37] at the discretion of the investigator, or otherwise guided by local rheumatologic, orthopaedic, or radiologic expert advice. Where Kellgren and Lawrence grading is used for the radiographic evaluation of major joint OA, grade ≥2 would be considered exclusionary for trial participation. In subjects for whom there is evidence of clinically significant sensory impairment in the distal lower extremity (based on medical history, clinical examination, TNSn, or evidence of sensory nerve conduction impairment available from NCS), there is an absolute requirement for bilateral feet and ankle radiographs to be undertaken for the evaluation of OA severity to exclude the possibility of neuropathic arthropathy. All radiologic investigations should be reported locally and the reports should be retained in the patient files as source documentation and made available in the event that subsequent adjudication of rheumatologic adverse events is required. Radiologic images should also be retained and made available in the event that subsequent adjudication of rheumatologic adverse events is required.
12. Chronic pain condition, other than PDN, that is likely to interfere with the evaluation of the subject's PDN pain, as judged by the investigator.

13. Presence of any major psychiatric disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, if, in the opinion of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect pain assessment, or affect the subject's ability to complete the study.
14. Significant cardiovascular disease, including Class 3 or Class 4 (The Criteria Committee of the New York Heart Association (NYHA) classification standards 1994)[38] congestive heart failure (ejection fraction of <40%) or clinically significant stenosis or occlusion of a carotid or vertebral artery or clinically significant arrhythmias.

    NOTE: Validated NYHA classification standards:

    - Class 1: cardiac disease but no symptoms and no limitations in ordinary physical activity (no shortness of breath when walking, climbing stairs)
    - Class 2: mild symptoms (mild angina or shortness of breath) and slight limitation with ordinary physical activity
    - Class 3: marked limitation due to symptoms, even during less than ordinary activities such as walking 20 to 100 meters; comfortable only at rest
    - Class 4: severe limitations and symptoms at rest

      NOTE: Subjects designated as NYHA functional Class 1 or Class 2 are not necessarily excluded from participation. However, such subjects should have left ventricular ejection fraction measured by echocardiography and documented at baseline
15. Significant or chronic lung disease, including severe or unstable chronic obstructive pulmonary disease (COPD), or severe or unstable asthma.
16. Known or suspected systemic infection, including HIV, HBV, hepatitis C virus (HCV), or TB as judged by the investigator or from screening testing. At screening, a QuantiFERON test will be conducted for TB (Nyendak et al. 2009; Duarte et al. 2012; Cush et al. 2010).[39,40,41]
17. History or evidence of any significant autoimmune disease or disorder, including inflammatory bowel disease, multiple sclerosis, or systemic lupus erythematosus.
18. History of severe allergy/hypersensitivity reactions or history of hypersensitivity to immunisations or immunoglobulins.
19. History of cancer within **5 years** of screening or between screening and randomisation, with the exception of non-metastatic basal cell carcinoma of the skin, carcinoma in situ of the cervix, or non-progressive prostate cancer.
20. Transient ischaemic attack or stroke in the last **3 years**.
21. History of alcohol or recreational drug dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria, within **2 years** of screening, with the exception of nicotine dependence, which is permitted.

    NOTE: Where there is a documented or suspected history of excessive alcohol usage or recreational drug usage, it is expected that the impact of this with respect to risk be evaluated at screening using the appropriate quantitative or semi-quantitative methodologies according to local standards of accepted medical or psychiatric practice. For example, use of the Fast Alcohol Screening Test (FAST) and Alcohol Use Disorders Identification Test (AUDIT)

alcohol screening questions for the initial evaluation of harm and risk associated with excessive alcohol consumption.

22. Within **1 year** of screening or between screening and randomisation, any of the following: myocardial infarction, hospitalisation for unstable angina or arrhythmia, or unexplained syncope.
23. Clinically important infection, including chronic, persistent, or acute infection, within **3 months** of screening or between screening and randomisation.
24. **Current** serious or unstable clinically important illness, including avascular necrosis, respiratory, cardiovascular, gastrointestinal, endocrinologic (excluding well-controlled type 1 or type 2 diabetes), immunologic, haematologic, neurologic, or other major disease that is likely to deteriorate or affect the subject's safety or ability to complete the study, as judged by the investigator.

Procedural contraindications

25. Any significant medical or surgical procedure or trauma within **28 days** of Day 1, or planned to be undertaken within the timeframe of the clinical trial, that will likely affect the subject's safety or ability to complete the study, or the scientific integrity of the study data, as judged by the investigator.

Physical and neurological examination, vital signs, ECG, laboratory values, and imaging

26. Clinically important abnormality in the physical and neurological examination, vital signs, or clinical laboratory test at screening that could affect the subject's safety or ability to complete the study, or the integrity of the clinical trial data, as judged by the investigator.
27. Poorly controlled hypertension (defined as systolic blood pressure [SBP] of >165 mmHg and/or diastolic blood pressure [DBP] of >95 mmHg measured in the clinic) or orthostatic hypotension (defined as a sustained reduction of SBP of at least 20 mmHg and/or a DBP reduction of at least 10 mmHg within 3 minutes of standing from a supine position). *Note:* If the blood pressure (BP) measured in the clinic is out of range, the measurements can be repeated on the same day or at another convenient visit.
28. Prolonged QTcF of >470 msec or family history of long QT syndrome, or shortened QTcF of <360 msec or family history of short QT syndrome, or any clinically significant abnormality in ECG rhythm, conduction, or morphology, including but not limited to:
    - PR/PQ interval prolongation (PR/PQ >220 ms)
    - intermittent second or third degree atrioventricular (AV) block (AV block II Mobitz Type I, Wenckebach, while asleep or in deep rest is not exclusionary)
    - bundle branch block (BBB) or intraventricular conduction delay (IVCD) with QRS duration >120 ms
29. Haemoglobin A_1C greater than 10.0% (>10.0%).
30. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >1.5 × the upper limit of normal (ULN) at screening or between screening and baseline. If the enzyme is >1.5 × ULN, the investigator can either exclude the subject at that time or decide to repeat the test once. If the repeat result is still >1.5 × ULN, the subject must be excluded.

31. Screening creatinine clearance of <60 mL/min as determined by the Cockcroft-Gault formula.
32. Clinically significant abnormal findings in coagulation or haematology laboratory tests, as judged by the investigator.
33. A positive pregnancy test at screening. (If the screening urine pregnancy test is more than 7 days before the first day of treatment, it must be repeated prior to the first dose.)
34. Positive drug screen for drugs of abuse (including but not limited to amphetamine, barbiturate, cannabinoids, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene), **unless** there is a documented medical explanation for the positive result other than drugs of abuse (eg, the subject takes opioids under medical supervision for pain and the prescribed opioid dosing regimen is expected to be stable and unchanged for the duration of the study; or where cannabinoids are similarly being taken for documented medical reasons).

8.3 Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the case report form (CRF) or electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.4 Subject Replacement Criteria

Withdrawn subjects may be replaced if withdrawal occurs at, or prior to, the Week 2 visit.

9 TREATMENTS

9.1 Identification of Investigational Products

The products that will be used in this study are outlined in Table 9-1.

Table 9-1: Identification of Investigational Product

Product	Strength and dosage form	Manufacturer/Supplier
MEDI7352	CCI	
Solvent for reconstitution of MEDI7352		
Diluent for reconstituted MEDI7352 and placebo		
IV bag protectant		

CCI

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9.1.1 Dose, Route of Administration, and Dosing Schedule

Once randomized, subjects will be dosed with either MEDI7352 or placebo on Day 1, Day 14, Day 28, Day 42, Day 56, and Day 70. MEDI7352 or placebo will be administered IV over a 60-minute period.

MEDI7352 or placebo should be administered by the investigator or site personnel prepared to manage infusion reactions and anaphylaxis. The infusion rate may be slowed or interrupted if the subject develops an infusion reaction. [NOTE: If the infusion is slowed or interrupted, the total infusion time should not exceed 4 hours at room temperature.] Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor subjects closely. In the event of a serious reaction, MEDI7352 or placebo administration must be discontinued immediately and the appropriate medical therapy administered.

Subjects will be dosed as outpatients but should remain under clinical supervision and should be monitored for no less than 4 hours after completion of each infusion. Should clinical features of acute hypersensitivity occur, an extended period of monitoring in an appropriate environment may be relevant, based on clinical judgement. This may include, but is not necessarily limited to, monitoring vital signs and observing for any untoward reactions. Consultation with the appropriate local clinical services may be warranted (eg, high dependency or intensive therapy unit).

Subjects should be made aware of the potential risks of acute hypersensitivity and infusion-related reactions, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention should they occur.

9.1.2 Current Treatment of Painful Diabetic Neuropathy

Subjects should currently be taking medication for the treatment of PDN. Subjects should be taking at least one of the first-line medications (consistent with regional or local standard of care guidelines for PDN) belonging to *either* the anticonvulsant class (pregabalin or gabapentin) *or* the antidepressant class (duloxetine, venlafaxine, or amitriptyline), but no more than one medication from a single class. Subjects receiving treatment with opioids alone (as a monotherapy) should be excluded, *unless* the opioids are being prescribed as a second-line treatment for PDN because the first-line therapies were found to be poorly tolerated or not efficacious. For all drug classes, subjects should be established on a stable dosing regimen that is consistent with regional or local standards of accepted prescribing practice for no less than 3 months before the anticipated randomisation date. Subjects should be willing to maintain this stable dosing regimen for the duration of study participation until the last follow-up visit.

9.1.3 Rescue Medication

Subjects who develop unacceptable pain during any stage of the study (including during the washout period prior to randomisation) will be permitted to initiate rescue analgesic therapy with paracetamol up to a maximum dose of two 500 mg tablets (ie, 1 g per dose) up to 4 times daily (ie, 4 g per 24-hour period).

If paracetamol does not relieve the subject's pain, they may receive stronger analgesics as rescue medication (including tramadol and other 'weak' opiates) at the investigator's discretion and in consultation with the medical monitor.

Subjects may use sedative/hypnotics (eg, benzodiazepines) on a pro re nata (PRN; where necessary) basis, but these should not be taken more than 3 times a week or within 24 hours of a

clinic visit and such use will be considered a protocol deviation. Prohibited therapies are listed in Section 9.7.2. Other restrictions are listed in Section 9.7.3.

As a guideline, rescue medication should not generally be given for more than 3 consecutive days. All rescue medication use must be captured in the CRF and subjects will be required to record reasons for use.

The study site will not supply rescue medication.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

9.2 Selection of Timing of Dose for Each Subject

The 2-weekly dose interval has been chosen based on PK, PD (NGF suppression) and efficacy considerations. In the first-in-human study in subjects with OA, the dosing schedule was 2-weekly, and preliminary (blinded) data indicated that the effect of MEDI7352 on OA pain was detectable for 2 weeks.

9.3 Dose Adjustment Criteria

Dose adjustment is not allowed in this study. Subjects will be allocated to a single dosing regimen at randomisation.

9.3.1 Safety Stopping Rules

Safety will be monitored by the study-appointed medical monitors from Premier Research and AstraZeneca throughout the study in accordance with the Medical Monitoring Plan. In addition, an Interim Safety Review of blinded aggregate safety data will be undertaken following completion of follow-up visits for approximately every 30 subjects enrolled in the study and no less frequently than every 3 months. The interim review will be performed by AstraZeneca Neuroscience in conjunction with the pharmacovigilance and safety agent, MMS Holdings in accordance with the Safety Management Plan.

Based on the interim safety reviews of aggregate safety data, the study may be stopped if the risks are found to outweigh the potential benefits.

For any individual subject, further administration of IP will be stopped if any of the following scenarios occur with a reasonable possibility of a causal relationship to administration of MEDI7352:

- Reports of drug-related serious AE (SAE[s]) or drug-related severe AE(s) including (but not necessarily limited to):
    - Infusion reactions and injection site reactions
    - Worsening of existing cutaneous sensory abnormalities or development of new cutaneous sensation AEs (eg, paraesthesia, dysesthesia, burning, pins and needles) that are considered serious or severe and drug-related
    - Positively adjudicated destructive arthropathy
    - Serious systemic infection

- Anaphylactic reaction, defined as an immediately life-threatening allergic reaction with bronchoconstriction, angioedema, and/or hypotension (refer to FDA Guidance for Industry, Immunogenicity assessment for therapeutic protein products, 2014).[42]
- Fulfilling Hy's Law, defined as AST or ALT ≥3 × ULN and bilirubin ≥2 × ULN, in the absence of a significant increase in alkaline phosphatase (ALP) and in the absence of an alternative diagnosis that could explain the increase in bilirubin
- Severe autonomic AEs, including but not limited to symptomatic orthostatic hypotension and orthostatic intolerance, that are considered drug-related
- Renal toxicity, defined as serum creatinine ≥1.5 × ULN
- Haematologic toxicity, defined as one or more of the following:
  - Leukocyte count $<2.0 \times 10^9$/L
  - Neutrophil count $<1.0 \times 10^9$/L
  - Platelet count $<75 \times 10^9$/L

9.4 Treatment Compliance

All subjects will receive the IP infusion at the study site under the surveillance of appropriate study personnel. Infusion details will be recorded in the subject's eCRF.

9.5 Method of Assigning Subjects to Treatment Groups

The randomisation schedule will be computer generated using a permuted block algorithm appropriate to the treatment groups included in each stage and will randomly allocate IP to randomisation numbers. The randomisation numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. The randomisation schedule will not be stratified and study center will not be a blocking factor in the randomisation schedule.

The randomisation schedule will be prepared by Premier Research before the start of the study. No one involved in the study performance will have access to the randomisation schedule before official unblinding of treatment assignment. No subject will be randomised into this study more than once.

9.6 Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code, unblinded site monitors and clinical manager from Premier Research, and the unblinded pharmacist at each study site. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel. Unblinded personnel who are not otherwise involved in the study will prepare data for review and interim analysis.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, study personnel will use the IWRS. Only authorized users will have access to the unblinding function in the IWRS, and the IWRS will reveal the treatment information for the selected subject only. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The IWRS will also send a blinded notification to the clinical team alerting them that a break blind occurred.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate CRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she will be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

Overall unblinding will take place at the end of the study only after database lock has been achieved.

9.7 Permitted and Prohibited Therapies

All concomitant medications used (including OTC medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.7.1 Permitted Therapies

As detailed in Section 9.1.2, subjects should continue to take their prescribed medication for the treatment of PDN.

The following medications are permitted during the study, with restrictions:

- Subjects who develop unacceptable pain due to PDN or other conditions (eg, headache, muscular pain, etc.) during any stage of the study (including during the washout period prior to randomisation) will be permitted to initiate rescue/analgesic therapy with paracetamol up to a maximum dose of two 500 mg tablets (ie, 1 g per dose) up to 4 times daily (ie, 4 g per 24-hour period).
- As a guideline, rescue medication should not generally be given for more than 3 consecutive days. All rescue medication use must be captured in the CRF and subjects will be required to record reasons for use. Subjects will be requested not to take any rescue therapy within 24 hours of a clinic visit.
- If paracetamol does not relieve the subject's PDN pain, they may receive stronger analgesics as rescue medication (including tramadol and other 'weak' opiates) at the investigator's discretion and in consultation with the medical monitor.
- Subjects may use sedative/hypnotics (eg, benzodiazepines) on a PRN basis, but these should not be taken more than 3 times a week or within 24 hours of a clinic visit.
- Low dose aspirin for cardiovascular prophylaxis.

- If the subject is receiving permitted medications for the treatment of non-excluded medical conditions (eg, antihypertensive medication, cholesterol-lowering treatment, antidiabetic medication), the dose and dosing regimen must be stable for at least 28 days before randomisation and should be expected to remain stable for the duration of study participation until at least the last follow-up visit.
- Other medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator (eg, a regular prescribed treatment regimen for glycaemic control in the management of diabetes; antihypertensive medication).

9.7.2 Prohibited Therapies

The following therapies are prohibited during the study:

- NSAIDs or analgesic doses of aspirin (325 mg/day or higher). The subject must be willing and able to discontinue all NSAID or COX-2 analgesic therapy from the start of the washout period until the end of follow-up. This includes OTC pain medications and topical analgesics that contain an NSAID or COX-2 inhibitor. The use of NSAIDs (eg, ibuprofen, naproxen) or COX-2 medications (eg, celecoxib) at any time during the study and through to completion of drug washout (5 half-lives) is prohibited and contraindicated.
- Any other investigational drug or device, including other immunotherapeutics and live viral or attenuated bacterial vaccines.
- Any drug of abuse including but not limited to: amphetamine, barbiturate, cannabinoids, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene, **unless** there is a documented medical explanation other than drugs of abuse (eg, the subject takes opioids under medical supervision for pain and the prescribed opioid dosing regimen is expected to be stable and unchanged for the duration of the study; or where cannabinoids are similarly being taken for documented medical reasons); or sedative/hypnotics used as described above.
- Muscle relaxants, anticonvulsants, anti-Parkinsonian medications, or neuroleptic medications, unless used for non-excluded conditions such as Restless Leg Syndrome or as an adjuvant for pain on a regular schedule.
- Oral, IV, intramuscular, or any other parenteral steroids (inhaled steroids for well-controlled COPD or asthma, or topical steroids for eczema, are permitted).
- Treatment with another biologic therapeutic agent.

The following therapies are prohibited both before and during the study:

- Previously received any form of anti-NGF or anti-TNF therapy.
- Participation in another clinical study with an IP or device within 60 days or 5 half-lives prior to screening, whichever is longer.
- Any significant medical or surgical procedure or trauma within 28 days of Day 1, or planned to be undertaken within the timeframe of the clinical trial, that will likely affect the subject's safety or ability to complete the study, or the scientific integrity of the study data, as judged by the investigator.

Subjects receiving excluded therapies will be ineligible for study enrolment or for continuation in the study, at the discretion of the investigator.

9.7.3 Restrictions

- Subjects will be asked to avoid foods containing poppy seeds for 5 days prior to the screening visit.
- Subjects will be asked to avoid any changes in OTC products and herbals, vitamins, and minerals from at least 14 days before first dosing on Day 1 through to the end of follow-up. If needed, a nasal spray for nasal congestion may be used occasionally. If a change in concomitant medication is needed, the investigator must decide if the subject should remain in the study or be dismissed from the study.
- Subjects who use nicotine patches or other nicotine formulations may continue to use them at the same dose regimen.
- Subjects must refrain from blood and plasma donation during the study and up to 2 months after the final follow-up visit.
- Male subjects must use appropriate contraception (see Appendix B) and must refrain from sperm donation from first dosing on Day 1 until at least 3 months after the last dose.
- Discharge from the clinical unit after administration of study drug may be delayed for safety reasons at the discretion of the investigator.

9.8 Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.9 Dispensing and Storage

AstraZeneca will provide the investigators with adequate quantities of MEDI7352 using designated distribution centers. Pharmacy personnel will prepare all the IPs for each subject according to handling instructions provided by AstraZeneca and the randomisation scheme.

The IP supplied by AstraZeneca is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator (or designee) must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at AstraZeneca and/or Premier Research. CCI [redacted]

9.10 Drug Accountability

The investigator (or designee) must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IPs. The investigator will not supply the IP to any person except those named as sub-investigators, designated study personnel, and subjects in this study. The investigator will not dispense the IPs from any study sites other than those authorized. Investigational product(s) may not be relabelled or reassigned for use by other

subjects. If any of the IPs are not dispensed, are lost, stolen, spilled, unusable, or are received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, the IPs (partly used, unused, and empty packaging) must be left in the original packaging until the study site has been instructed in writing to either destroy the IP according to approved procedures or to return the IP to the sponsor or designee for destruction.

9.11 Labelling and Packaging

9.11.1 Labelling

Each vial of IP will have a label affixed that meets the applicable regulatory requirements and may include the following: IP name/study drug, dosage form, directions for use including route of administration, protocol number, regulatory statements if required, storage conditions, expiry date, and sponsor identification. Each IP kit will have a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial will be labelled with the same unique sequence number range.

Final labelling will comply with the regulatory requirements of each country where the study will be conducted.

9.11.2 Packaging

CCI [redacted]

10 STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Table 2-1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1 Study Duration

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening: 45 days
2. Treatment: 12 weeks
3. Follow-up: 42 days

The maximum treatment duration for each subject is approximately 12 weeks.

The maximum study duration for each subject is approximately 25 weeks.

10.2 Study Periods and Visits

The study consists of a total of 11 visits: 1 (or more) screening visit(s), 6 treatment visits, 2 visits solely for blood draws, an end-of-treatment visit, and a follow-up visit.

10.2.1 Screening and Washout

10.2.1.1 Screening

The subject must be screened within 45 days before enrolment in the study and at least 7 days before the first day of treatment to allow for 7 days of baseline pain ratings. Screening procedures may be performed at 1 or more visits. The following procedures will be performed at screening:

1. Obtain written informed consent.
2. Assess inclusion/exclusion criteria.
3. Collect demographic information.
4. Record medical history, including current therapies (eg, prescription and non-prescription medications).
5. Perform a complete physical and neurological examination (excluding the genitourinary examination, unless warranted), including weight and height.
6. Measure vital signs in supine position (HR, BP [in supine position after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of BP and pulse 1 minute (>1 minute, <3 minutes) after the subject stands.
7. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.
8. Perform motor and sensory NCS.

9. Perform TNSn, strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments.
10. Collect blood sample for the following:
    - serology (HIV, hepatitis B and C, and TB [QuantiFERON] testing)
    - chemistry, haematology, and coagulation
    - hemoglobin A_1c
    - immunogenicity (ADA) testing
    - pharmacogenetic testing (optional)
11. Collect urine sample for the following:
    - urinalysis
    - urine drug screen
    - urine pregnancy test (for women who are not surgically sterile) (If the screening urine pregnancy test is more than 7 days before the first day of treatment, it must be repeated prior to the first dose)

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12. Perform Galer NPS.
13. Perform SF-36.
14. Train the subject on rating their daily pain and DSIS, and entering these data into the electronic patient-reported outcome (ePRO) system. To determine eligibility, pain scores from Days -7 to -1 are required.
15. CCI

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.2 Double-blind Treatment Period (Days 1-84 [Weeks 1-12])

The treatment period consists of 6 treatment visits every 2 weeks (from Day 1 to Day 70), 2 blood draw visits on Days 71 and 77, and an end-of-treatment visit on Day 84 (2 weeks after the last dose).

10.2.2.1 Day 1 (Treatment 1)

The timing of safety assessments and safety blood sampling on Day 1 is presented in Table 2-2.

The following procedures will be performed on Day 1 before treatment with the IP:

1. Record AEs and concomitant medications and therapies.
2. Perform a targeted physical and neurological examination.
3. Perform TNSn, strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments.

4. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.
5. Measure supine vital signs (HR, BP [supine after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of BP and pulse 1 minute (>1 minute, <3 minutes) after the subject stands.
6. Confirm that all inclusion/exclusion criteria are satisfied.
7. Assign a randomisation number via IWRS. If necessary, the randomisation transaction in IWRS can be performed on Day -1. [Note: Subjects who have been randomised in the IWRS, but who do **not** receive a subsequent dose and do not continue study participation, will be classified as Early Terminated Subjects].

The following procedures will be performed on Day 1 after randomisation:

8. Collect pre-dose blood samples for the following:
   - chemistry, haematology, and coagulation
   - CCI [redacted]
   - PK
9. Collect urine sample for urinalysis.
10. Administer the IP infusion.
11. Repeat 3 replicates of ECGs (with printouts) at 60 (±10) minutes after the start of IP administration, and 2 and 4 hours (±10 minutes) after the start of IP administration. Subjects must rest in the supine position for 10 minutes prior to each ECG recording session.
12. Vital signs measurements. Assess **supine blood pressure and heart rate** at 15 mins, 30 mins, 45 mins, 60 mins (within 10 minutes of infusion end), 2 hours, and 4 hours after start of infusion. **Orthostatic vital signs** (standing heart rate and BP) should be measured at 60 mins (within 10 minutes of infusion end), 2h and 4h after start of infusion. These orthostatic measurements should be taken **after** the supine measurements and **after** the subject has adopted the standing position for 1 minute (>1 minute, <3 minutes). Assess **body temperature** at 60 mins, 2h and 4h after start of infusion. Assess **respiratory rate** at 15 mins, 60 mins, 2 hours, and 4 hours after start of infusion. [Note: unless where stated, an acceptable window for measurement of vital signs is ± 5 minutes in relation to the specified time-point].
13. Assess the IV injection site for local reactions at 15 mins, 30 mins, 45 mins, 60 mins, 2 hours, and 4 hours after start of infusion.
14. Assess and record any AEs occurring during the visit.
15. Remind the subject to continue entering their daily pain and DSIS into the ePRO system and rescue medication into the paper diary.

10.2.2.2 Days 14, 28, 42, 56, and 70 (Treatments 2 to 6)

The following procedures will be performed on Days 14, 28, 42, 56, and 70:

1. Perform Galer Neuropathic Pain Scale (NPS) **(Days 28 and 56 only)**.
2. Perform PGIC **(Days 28 and 56 only)**.
3. Perform a targeted physical and neurological examination.
4. Perform TNSn, strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments.
5. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes **(Days 28 and 56 only)**.
6. Measure pre-dose sitting vital signs (HR, BP [sitting after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of BP and pulse 1 minute (>1 minute, <3 minutes) after the subject stands.
7. Collect pre-dose blood samples for the following:
   - chemistry, haematology, and coagulation
   - immunogenicity (ADA) testing **(Days 14, 28, 56, and 70 only)**
   - CCI [redacted]
   - PK
8. Collect urine sample for the following:
   - urinalysis

CCI [redacted]

9. Administer the IP infusion.

CCI [redacted]

11. Five (5) minutes (± 5 minutes) after completion of the infusion, repeat **sitting vital signs** (HR, BP [sitting after a 5-minute rest], respiratory rate, and temperature). **Orthostatic vital signs** (standing heart rate and BP) should be measured at 5 minutes (± 5 mins) after completion of the infusion. These orthostatic measurements should be taken **after** the sitting measurements and **after** the subject has adopted the standing position for 1 minute (>1 minute, <3 minutes).
12. Assess the IV injection site for local reactions.
13. Approximately 8 hours (± 15 mins) after the start of the infusion, collect a blood sample for the following (**Day 70 only**):
    - PK
    - CCI [redacted]
    - CCI [redacted]
14. Record AEs and concomitant/rescue medications and therapies.

15. Remind the subject to continue entering their daily pain and DSIS into the ePRO system and rescue medication into the paper diary.
16. Schedule the subject to return to the clinic for the next visit (on Day 70, schedule the subject to return to the clinic for the 24-hour blood sample).

10.2.2.3 Day 71

1. Measure sitting vital signs (HR, BP [sitting after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of blood pressure and pulse 1 minute (>1 minute, <3 minutes) after the subject stands.
2. Approximately 24 hours (± 4 hours) after the start of the Day 70 infusion, collect a blood sample for the following:
   - PK
   - CCI [redacted]
   - CCI [redacted]
3. Record AEs and concomitant/rescue medications and therapies.
4. Schedule the subject to return to the clinic for the Day 77 blood sample at approximately the same time of day as the Day 70 infusion.

10.2.2.4 Day 77

1. Measure sitting vital signs (HR, BP [sitting after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of blood pressure and pulse 1 minute (>1 minute, <3 minutes) after the subject stands.
2. At approximately the same time of day (± 4 hours) as the Day 70 infusion, collect a blood sample for the following:
   - PK
   - CCI [redacted]
   - CCI [redacted]
3. Record AEs and concomitant/rescue medications and therapies.
4. Schedule the subject to return to the clinic for the Day 84 visit.

10.2.2.5 Day 84 (End-of-treatment; Week 12)

The following procedures will be performed at the end-of-treatment visit on Day 84 (2 weeks after the last dose):

1. Perform Galer NPS.
2. Perform PGIC.
3. Perform SF-36.
4. Perform a complete physical and neurological examination (excluding the genitourinary examination, unless warranted).

5. Perform TNSn, strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments.
6. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.
7. Measure sitting vital signs (HR, BP [sitting after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of blood pressure and pulse 1 minute (>1 minute, <3 minutes) after the subject stands.
8. Collect blood samples for the following:
   - chemistry, haematology, and coagulation
   - immunogenicity (ADA) testing
   - PK
   - CCI
9. Collect urine sample for the following:
   - urinalysis
   - urine pregnancy test (for women who are not surgically sterile)

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10. Assess the IV injection site for local reactions.
11. Record AEs and concomitant/rescue medications and therapies.
12. Remind the subject to continue entering their daily pain and DSIS into the ePRO system and rescue medication into the paper diary.
13. Schedule the subject to return to the clinic for the Week 18 visit.

10.2.3 Follow-up (or Early Termination) Evaluation (Week 18)

At 6 weeks after the last visit (8 weeks after the last administration of the IP) or upon early termination of the study, the following procedures will be performed:

1. Perform Galer NPS.
2. Perform PGIC.
3. Perform a complete physical and neurological examination (excluding the genitourinary examination, unless warranted).
4. Perform TNSn, strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments.
5. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.
6. Perform motor and sensory NCS.
7. Collect blood samples for the following:
   - chemistry, haematology, and coagulation

- immunogenicity (ADA) testing
- PK and CCI [redacted] (only if this is an Early Termination Visit)

8. Collect urine sample for the following:
   - urinalysis
   - urine pregnancy test (for women who are not surgically sterile)

CCI [redacted]

9. Measure sitting vital signs (HR, BP [sitting after a 5-minute rest], respiratory rate, and temperature). To assess orthostasis, repeat the measurement of BP and pulse 1 (>1 minute, <3 minutes) minute after the subject stands.
10. Assess the IV injection site for local reactions.
11. Record AEs and concomitant medications and therapies.

10.3 Assessments

10.3.1 Efficacy Variables

Efficacy will be assessed by daily average pain, as measured on an 11-point (0-10) NRS; the Galer NPS the DSIS; the PGIC; and the SF-36. CCI [redacted] The time points for each assessment are listed in Schedule of Events (Table 2-1).

10.3.1.1 Numerical Rating Scale

Subjects will assess their perceived average neuropathic pain over the previous 24 hours using an 11-point NRS, with 0 representing no pain and 10 representing the worst pain imaginable. Subjects will be instructed to assess their average daily pain at approximately the same time every morning, and to record their response in a subject diary (ePRO).

10.3.1.2 Galer Neuropathic Pain Scale

Subjects will assess their neuropathic pain using the Galer NPS. The NPS includes 2 descriptors of pain, including intensity and unpleasantness, and 8 descriptors that assess specific qualities of neuropathic pain: sharp, hot, dull, cold, sensitive, itchy, deep, and surface pain. Each of these 10 dimensions has a 0 to 10 NRS in which 0 is equal to no pain and 10 equals the most intense pain.

10.3.1.3 Daily Sleep Interference Scale

Subjects will assess how their neuropathic pain interferes with their sleep using the DSIS. The DSIS is an 11-point Likert scale, with 0 indicating that pain did not interfere with sleep and 10 indicating that pain completely interfered with sleep. The DSIS is completed by subjects once a day (upon awakening) to accurately capture variability in sleep interference due to pain on a daily basis, thus minimizing recall bias.

10.3.1.4 Patient Global Impression of Change

Subjects will rate their overall improvement in health status using the PGIC. The PGIC consists of a 7-point scale where 1 = "very much improved" and 7 = "very much worse". Subjects will be asked the following question: "How would you rate your overall improvement with treatment during the clinical study?" The response options include the following:

Very Much Improved	1
Much Improved	2
Minimally Improved	3
No Change	4
Minimally Worse	5
Much Worse	6
Very Much Worse	7

10.3.1.5 Short-Form Health Survey

The subject's health status and quality of life will be assessed using the SF-36.

The SF-36 assesses 8 health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The items use Likert-type scales with either 5 or 6 points, or 2 or 3 points.

10.3.1.6 Rescue Medication Use

Subjects will record all rescue medications they take for neuropathic pain in a paper diary.

10.3.1.7 CCI

CCI

[redacted]

10.3.2 Clinical Pharmacology

Samples will be collected at the time points specified in the Schedule of Events (Table 2-1).

10.3.2.1 Pharmacokinetic Analysis Methods

The PK characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA). Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the C_{max} and T_{max}. The following PK parameters will be determined:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Apparent first order terminal elimination half-life ($t½$)
- Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration (AUC_{0-t})
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)
- AUC_{tau} at steady state
- C_{max} at steady state
- Volume of distribution at steady state
- Apparent total body clearance at steady state (CL_{ss})

Actual sampling times will be used for all PK parameter estimation.

Additional details of the parameters and their calculation and evaluation will be included in the SAP.

10.3.2.2 Pharmacodynamic Variables

Plasma or serum samples will be collected for exploration of free and/or total NGF.

10.3.2.3 Pharmacogenetic Variables

Pharmacogenetic analysis is optional. If a subject declines to participate in the genetic research, this will have no influence on the ability of the subject to participate in the study.

CCI [redacted]

10.3.2.4 CCI [redacted]

CCI [redacted]

Samples will be analysed using a validated analytical method in compliance with AstraZeneca's standard operating procedures and analytical requirements.

CCI

[redacted]

10.3.2.5 Immunogenicity

Blood samples will be collected for assessment of ADA levels.

10.3.3 Safety Variables

Safety assessments will include the evaluation of AEs, clinical laboratory tests, vital signs, 12-lead ECGs, physical and neurological examination findings, neuropathy assessments (TNSn), strength (dorsiflexion), and deep tendon reflex (knee and ankle) assessments, motor and sensory nerve conduction, concomitant medications, injection site reactions, and infusion reactions.

10.3.3.1 Clinical Laboratory Assessments

10.3.3.1.1 Clinical Laboratory Tests to be Performed

Samples for laboratory tests will be collected at the time points specified in the Schedule of Events (Table 2-1) and will include the following:

Haematology:	hemoglobin, haematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, ALP, ALT, AST, blood urea nitrogen, creatinine*, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, C-reactive protein (CRP) *serum chemistry reports should include calculation of creatinine clearance using the Cockcroft-Gault equation for estimation of GFR (eGFR)
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood urine, glucose, protein, ketones
Pregnancy Test [urine]:	for women who are not surgically sterile
Urine Drug Screen:	including but not limited to amphetamine, barbiturate, cannabinoids, cocaine, methadone, methaqualone, opiate, phencyclidine, and propoxyphene
Serology:	HIV, hepatitis B and C, and tuberculosis (QuantiFERON)

Blood and urine samples for haematology, serum chemistry, urinalysis, and serology will be sent to a central laboratory for analysis. Urine drug screens and pregnancy tests will be conducted at the study sites.

10.3.3.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.3.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to AstraZeneca prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate CRF/eCRF.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.3.1.4 Clinical Examinations

10.3.3.1.5 Vital Signs

Vital signs (HR, BP, respiratory rate, and temperature) will be measured after the subject has been in a supine position for 5 minutes at screening and Day 1 and in a sitting position for 5 minutes at all other visits. To assess orthostasis, BP and pulse will be measured again 1 minute (>1 minute, <3 minutes) after the subject stands.

Vital signs will be assessed as follows:

- Screening: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in **supine** position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.
- Day 1 pre-dose: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in **supine** position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.
- Day 1 post-dose: **Supine and orthostatic** BP and HR at 15 mins, 30 mins, 45 mins, 60 mins, 2 hours, and 4 hours after start of infusion. Temperature and **supine and orthostatic** BP and HR at 60 mins, 2 hours, and 4 hours after start of infusion. Respiratory rate at 15 mins, 60 mins, 2 hours, and 4 hours after start of infusion. The 60-minute assessments should be performed within 10 minutes of the end of the infusion. [Note: An acceptable window for these vital sign assessments is ± 5 mins in relation to the specified time.]

- Days 14, 28, 42, 56, and 70 pre-dose: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in **sitting** position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.
- Days 14, 28, 42, 56, and 70 post-dose: 5 minutes after completion of infusion, measure respiratory rate, temperature, and HR and BP after a 5-minute rest in **sitting** position. After measuring sitting vital signs, assess orthostatic BP and HR 1 minute after the subject stands.
- Days 71, 77, and Week 18 or early termination: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in **sitting** position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.

10.3.3.1.6 Twelve-lead Electrocardiogram

All subjects will undergo ECGs as indicated in the schedule of assessments. Where applicable, digital ECGs will be collected using the ECG equipment delivered by the central ECG laboratory (ECG lab) and will be transferred to and analysed by the ECG lab according to the lab's standard operating procedures. Further details are provided in the ECG Manual.

Paper printouts of the 12-lead ECGs will be reviewed in real time by the principal investigator, or delegate, for safety monitoring. The results of the evaluation will be reported in the eCRF as *normal* or *abnormal* (if abnormal, the ECG is also to be reported as not clinically significant or clinically significant). The details of any ECG abnormalities should be described and captured in the eCRF (irrespective of whether they are considered not clinically significant or clinically significant).

10.3.3.1.7 Physical and Neurological Examination

A complete physical and neurological examination (excluding the genitourinary examination, unless warranted) will be performed at Screening, Week 12, and Week 18/Early Termination, as indicated in the schedule of assessments.

A targeted physical and neurological examination based on symptoms and previous findings will be performed at all other visits.

Height and weight will be measured at Screening.

10.3.3.1.8 Total Neuropathy Scores--Nurse

The TNSn, a semi-quantitative clinical assessment of peripheral nervous system function, will be administered at Screening, Day 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12 and Week 18/Early Termination. The TNSn provides for an assessment of motor symptoms, autonomic symptoms, pin sensibility, vibration sensibility, and deep tendon reflexes. Strength (dorsiflexion) and deep tendon reflexes (knee and ankle) are to be scored at every visit alongside the TNSn assessments.

10.3.3.1.9 Motor and Sensory Nerve Conduction Studies

Motor and sensory NCS will be undertaken in relevant lower and upper limb nerves (sural, peroneal, and median/ulnar nerves). Relevant endpoints including peak latency, amplitude, conduction velocity and duration of nerve action potentials will be captured using standard antidromic or orthodromic determination according to protocol and will be recorded at baseline and at the follow-up visit.

10.3.3.1.10 Injection Site or Infusion Reactions

Investigators should evaluate infusion reactions that occur during or immediately following infusion per the FDA Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products (2014) and FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).[42,43] See Section 5.3 for discussion of potential infusion reactions.

Investigators should evaluate injection site reactions using the toxicity grading scale summarized in Table 10-1.

Table 10-1: Local Reactions to Injectable Product

Local Reaction	Mild	Moderate	Severe
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness[a]	2.5 to 5 cm	5.1 to 10 cm	>10 cm
Induration/swelling[b]	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	>10 cm or prevents daily activity

Source: FDA 2007[43]

a In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

b Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

10.3.3.2 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with placebo, or during treatment-free periods of the study, are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an IP related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to an investigational product" means that a causal relationship between an IP and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is "possible" or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were "possible".

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a pre-approval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected AE or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IP or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

11.1.4 Serious Adverse Events

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

- results in death
- is life-threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

- results in persistent or significant disability/incapacity
- is a congenital anomaly

  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.

- is an important medical event

  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent if the first onset or worsening is after the first administration of IP and not more than 30 days after the last administration of IP.

11.2 Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The site staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Action(s) Taken

Action(s) taken may consist of:

Dose increased	An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount.
Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved

- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. [Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.]

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Related	A reasonable possibility exists of a relationship between the AE and IP.
Not related	No reasonable possibility exists of a relationship between the AE and IP.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the CRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (ie, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to MMS Holdings Inc. (MMS) within 24 hours of first becoming aware of the event by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to MMS by one of the following methods:

Email: drugsafety@mmsholdings.com

Fax number: +1 734 468 0850

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria that were met
- Concomitant medication at onset of the event

- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, AE, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the MMS Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to the sponsor according to the Safety Management Plan.

11.3 Special Considerations

11.3.1 Adverse Events of Special Interest

An AESI is a treatment-emergent AE of scientific and medical interest specific to understanding of the effects of the IP and may require close monitoring and collection of additional information by the investigator. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of MEDI7352.

Refer to Section 5.3 for a summary of potential risks and the IB for a detailed discussion of potential risks.

The following AESIs have been identified specifically for this MEDI7352 protocol and are to be reported as described in Section 11.2.6.1.

- Positively-adjudicated possible or probable RPOA, subchondral insufficiency fractures, primary osteonecrosis, or pathological fracture
- Infections that meet SAE or severe AE criteria*
- Anaphylactic reactions or infusion-related reactions that lead to permanent discontinuation of administration of IP

Adverse events of special interest irrespective of their severity and seriousness should be reported immediately using the same procedure as for SAE reporting (Section 11.2.6.1).

*Note: A serious infection is any infection that meets the SAE criteria in Section 11.1.4. Serious infection AEs should be reported as SAEs. A severe infection is any infection that does not meet SAE criteria but is incapacitating, with inability to perform normal activities. Non-serious severe infections are reported as AEs. It is expected that microorganism culture results and all diagnostic or therapeutic procedure results performed on a study participant experiencing a serious or severe infection will be provided as an SAE/AESI update.

11.3.2 Pregnancy

All women who participate in the study must be postmenopausal or surgically sterile. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman who is not surgically sterile. A woman who is found to be pregnant at the screening visit will be excluded from the study and considered to be a screening failure.

Men who are biologically capable of having children must agree and commit to use an adequate form of contraception (see Appendix B) for the duration of the treatment period and for 3 months after the last administration of study drug. A male subject is considered capable of having children even if his sexual partner is sterile or using contraceptives.

A woman who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately discontinued from study participation. The investigator must report the pregnancy as if it were an SAE within 24 hours of learning of the pregnancy, to MMS Pharmacovigilance using the Pregnancy Notification and Outcome Form via the same fax number and/or email address as for SAE reporting.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. The follow-up information must be reported to MMS Pharmacovigilance using a new Pregnancy Notification and Outcome Form. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

11.3.3 Overdose

The maximal dose of IP should not be exceeded during the study. The investigator must report any overdose to MMS PV within 24 hours of learning of the overdose using the Overdose Report Form provided by MMS PV. In case of known or suspected overdose, symptomatic treatment as well as monitoring of vital functions should be performed based on the judgment of the investigator. If the overdose does not result in an AE, it should be reported in written form to the designated individuals who receive SAE notification. The information contained therein should include study

site identification, reporter identification, subject identification, IP, dose, action taken (eg, supportive measures or therapy), and any comments.

12 DATA SAFETY MONITORING BOARD

A data safety monitoring board will not be used in this study.

13 STATISTICS

13.1 Statistical Analysis

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be finalized prior to database lock for the interim analysis.

Unless otherwise indicated, all formal testing of statistical significance will be one-sided, and a difference resulting in a 1-sided P value of ≤0.025 will be considered statistically significant. For estimation purposes, 2-sided 90% and 95% confidence intervals will be presented.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

13.1.1 Analysis Populations

The following 4 analysis populations are planned for this study:

- Screening: all subjects who provide informed consent and/or assent and provide demographic and/or baseline screening assessments, regardless of the subject's randomisation and treatment status in the study.
- Safety: The safety population will include all subjects who receive at least 1 dose of double-blind study medication.
- Modified intent-to-treat (mITT): The modified intent-to-treat population will be used for all efficacy analyses and will include all randomised subjects who receive at least 1 dose of double-blind study medication and have at least 1 post-baseline NRS assessment.
- PK: The PK population will include all subjects for whom a PK sample was obtained and analysed.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomised incorrectly or is administered the incorrect IP, analyses of the mITT population will be based on the IWRS-assigned treatment whereas all other analyses will be based on the actual treatment.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of subjects randomised, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

13.1.2.2 Protocol Deviations

Subjects who violate any inclusion and/or exclusion criteria or who have major protocol deviations during the study (such as incorrect treatment assignment or use of prohibited medications) will be summarised and listed.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations.

Demographic variables will be collected for any eventual analysis of differences in response to the IP, in accordance with local regulatory requirements. Baseline subject characteristics including medical history, physical and neurological examination findings, and other baseline disease history will be listed and included in summaries as appropriate.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms (PTs).

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each subject's total dose and number of infusions received. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group. In addition, any incomplete infusions will be listed.

13.1.4 Efficacy Analysis

All efficacy variables will be summarized descriptively including number of observations, mean, SD, minimum, median, and maximum for continuous variables, and frequency of observations in each category and percentage for categorical variables.

Primary and secondary endpoint efficacy data will be tabulated according to the 'Observed Cases' approach. In addition, if there is missing data at a key analysis time-point (Weeks 4, 8, and 12) then results will also be tabulated according to 'Last-Observation-Carried-Forward' (LOCF) and 'Baseline-Observation-Carried-Forward' (BOCF). For example, if an endpoint is missing from a post-randomisation visit then the last non-missing post-baseline endpoint recorded prior to the visit will replace the missing value. For endpoints with separate scales, if an individual scale item is missing then the item will be carried forward from the previous visits rather than the total score. For post-baseline diary data, if a subject has at least 4 out of 7 days' diary data prior to the visit, then this will be taken as a valid observed weekly average score. However, if a subject has 3 or fewer days of diary data, this will be counted as a missing weekly score, and the LOCF approach will carry forward the last 7 non-missing entries of the diary data prior to the visit in order to calculate the weekly mean score at endpoint score.

The main statistical analysis of the primary efficacy endpoint at Week 12 will use the multiple comparison procedure modelling (MCP-Mod) approach on LOCF data, which is a well-established statistical methodology for establishing both the existence of a dose response and modelling the underlying dose-response relationship. Both EMA (2014)[44] and FDA (2015)[45] have recognized MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase 2 dose finding studies under model uncertainty.

There are two steps to MCP-Mod:

1. The 'MCP' step is a rigorous method to establish presence of a dose response while protecting the type I error and, if the dose-response relationship is statistically significant, then
2. The 'MOD' step estimates the dose response function and associated model parameters, such as ED50 (the effective dose for 50% of the population) in the case of E_{max} relationship.

The MCP test will use linear contrasts corresponding to the five candidate models described in Section 13.2. The underlying model will be an analysis of covariance (ANCOVA) with dependent variable 'change from baseline to Week 12', and independent variables will include dose, 'baseline score' and co-medication type. The random error is assumed to be normally and independently distributed with constant variance.

If the MCP test is statistically significant, then the MOD step will select the most appropriate model from hyperbolic E_{max}, sigmoidal E_{max}, or linear using the 'E_{maxlin}' approach as described by Kirby et al. (2011).[46] From this model (including the same covariates as the ANCOVA model), various estimates will be derived (together with confidence intervals) of parameters of interest such as ED50, ED90, dose to achieve selected target effects, and model estimates of the treatment effect at doses studied.

In addition to the analysis of all stages combined, a supplementary analysis using an adaptive MCP-MOD method will be conducted where stages 2+3 and stage 4 will be analysed separately and the results combined using an inverse-normal p-value combination function, with weights related to the original planned sample sizes. Further details of the analysis will be included in the SAP.

To complement the MCP-MOD outputs, estimates and confidence intervals of each pairwise comparison versus placebo from the ANCOVA model described in the MCP step will be produced.

In addition, changes from baseline in continuous endpoints will be compared between treatment groups using mixed models repeated measures including terms for pooled site, treatment (as a factor), time point (as a factor), the interaction between treatment and time point, and the baseline value of the variable undergoing analysis. Binary outcomes will be analysed using generalized estimating equations, with the models including the same terms as the mixed models repeated measures. Other non-binary categorical endpoints will be analysed using Cochran-Mantel-Haenszel statistics. These analyses will be conducted on observed cases. Further details of the longitudinal modelling will be included in the SAP.

13.1.4.1 Efficacy Endpoints

The primary efficacy endpoint is the change in the weekly average of the average daily pain scores from the baseline week to Week 12, as measured on an 11-point (0-10) NRS.

The secondary endpoints are the following:

- Change in the weekly average of the average daily pain score, as measured on an 11-point (0-10) NRS, from baseline to Weeks 2, 4, 6, 8, and 10 of treatment and the week before the follow-up visit.
- Percentage of subjects who have achieved ≥30% and ≥50% reductions in the weekly average of the average daily pain score from baseline during Weeks 4, 8, and 12 of treatment and the week before follow-up.
- Change in Galer NPS from baseline to Days 28, 56, and 84 of treatment and the follow-up visit.
- Change in DSIS from baseline to Days 28, 56, and 84 of treatment and the follow-up visit.

- Proportion of subjects who have 'improved', 'much improved', or 'very much improved' relative to baseline on the PGIC on Days 28, 56, and 84 of treatment and the follow-up visit.
- Change in the SF-36 from baseline to Day 84 of treatment.
- Usage of rescue medication (yes/no) from baseline to Week 12 of treatment.

13.1.4.2 CCI

CCI

[redacted]

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics; graphical representations will also be provided. The PK parameters will be summarized by dose using descriptive statistics including geometric mean, geometric SD, arithmetic coefficients of variation, and geometric coefficients of variation. The potential relationships between PK and efficacy and safety parameters may be explored graphically. Statistical analyses of PK parameters will be outlined in the SAP. Subjects receiving placebo will not be included in the summary and analysis of PK parameters.

13.1.5.2 Pharmacodynamics

The PD variables (free and/or total NGF) will be summarized using descriptive statistics. The association between PD variables and efficacy endpoints will be explored. Further details will be included in the SAP.

13.1.5.3 CCI

CCI

[redacted]

13.1.5.4 CCI

CCI

[redacted]

13.1.5.5 Immunogenicity

Immunogenicity results will be listed and the effects of ADAs on PK and PD will be explored.

13.1.6 Safety and Tolerability Analyses

Safety and tolerability data will be summarised descriptively, including tables, listings, and graphs, as appropriate. Unless otherwise stated, descriptive summary statistics for continuous variables will include number of observations, mean (ie, arithmetic mean), SD, minimum, median, and

maximum. Descriptive summary statistics for categorical data will include frequencies and percentages.

13.1.6.1 Adverse Events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class and preferred term (PT). Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges, or other specific ranges of interest, will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte by treatment group and by study visit.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for SBP, DBP, HR, respiratory rate, and temperature.

13.1.6.4 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point. Abnormal results will be grouped as clinically significant and not clinically significant. A description of ECGs evaluated as abnormal will be provided.

If applicable (digital ECGs), descriptive summaries will be provided for measures provided by the ECG core laboratory from the digital ECGs for PR, QRS, QT, RR intervals and for the calculated variables QTcF and HR for each treatment group and time point.

13.1.6.5 Physical and Neurological Examination Findings

Physical and neurological examination findings will be listed.

13.1.6.6 Other Safety Assessments

Findings from other safety assessments (TNSn, strength (dorsiflexion), deep tendon reflexes (knee and ankle), motor and sensory NCS, and injection site reactions) will be listed and may be summarized if warranted.

13.1.7 Interim Analysis

Interim analyses are planned after approximately 60 subjects have completed at least 2 weeks of randomised treatment across placebo and CCI in stage 3. Unblinded personnel who are not otherwise involved in the study will prepare the data for review by an Interim Analysis Review Committee.

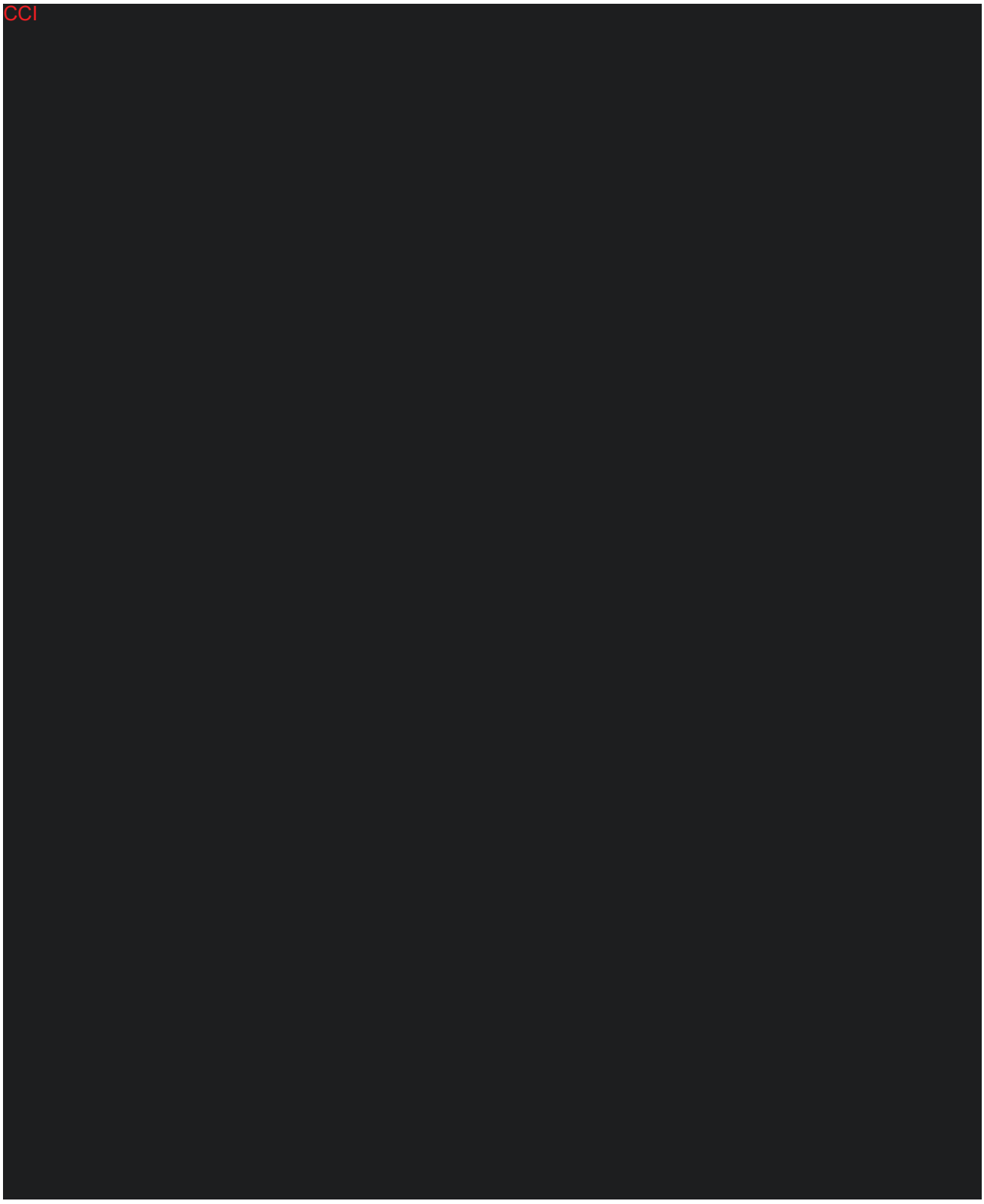
The members of the Interim Analysis Review Committee are independent of the day-to-day study activities. The study team will remain blinded to the results of the interim analysis for the duration of the study. Firewalls will be put in place to ensure that information is not inadvertently disseminated to the blinded members of the study team.

The primary aim of the analysis is to validate the key assumptions of the original sample size calculation, which could result in a recommendation to adjust the sample size (overall and/or to individual dose groups) or the treatment allocation ratio in stage 4. Further details of the sample size adjustment methodology will be included in an Interim Analysis SAP.

In addition, administrative analyses of efficacy data are planned to enable the sponsor to plan future project-related activities, but without making any changes to the design of the current study.

13.2 Sample Size Determination

CCI


CCI

14 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1 Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6.2).

AstraZeneca agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the April 1996 International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP), the Integrated Addendum to ICH E6 (R2) of November 2016, and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for overseeing the study closely and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that are/have been delegated study-related responsibilities (eg, sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing AstraZeneca with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information

generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

14.2 Site Initiation

Study personnel may not screen or enrol subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate regulatory authority and IRB/IEC approval for the protocol and the appropriate ICF.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3 Screen Failures

Subjects who do not meet the criteria for participation in this trial (screen failure) because of a laboratory result, disallowed medication, or other reversible condition may be rescreened at the discretion of the investigator.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4 Study Documents

All documentation and material provided by AstraZeneca for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol (ie, Investigator's Agreement)
- Curricula vitae of all investigators and sub-investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by AstraZeneca or its designee before the study site can initiate the study and before AstraZeneca will authorize shipment of IP to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to

ensure that copies of all required GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5 Data Quality Control

AstraZeneca and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

AstraZeneca and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associates (CRAs) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRAs and other authorized personnel access. The CRAs will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRAs will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow AstraZeneca or its designee's auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to the sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

14.5.2 Data Management

AstraZeneca or its designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by AstraZeneca or its designee. Audits may be performed to check compliance with GCP guidelines, and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (eg, protocol and/or clinical study report [CSR])

AstraZeneca or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be

available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify AstraZeneca immediately.

14.6 Study Termination

The study may be terminated at AstraZeneca's discretion at any time and for any reason.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, AstraZeneca or designee will notify the IECs and regulatory authorities of the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by AstraZeneca, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, AstraZeneca or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. AstraZeneca or its designee must clearly explain the reasons for premature termination.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination Visit.

14.7 Study Site Closure

At the end of the study, all study sites will be closed. AstraZeneca may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines

- Inadequate subject enrolment

14.7.1 Record Retention

After completing the study, AstraZeneca will receive the original CRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalysed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

With the participant's approval and as approved by local IRBs, de-identified biological samples may be stored with the same goal as the sharing of data. These samples could be used to research the causes of PDN, its complications and other conditions for which individuals with PDN are at increased risk, and to improve treatment. A code-link will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

14.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of AstraZeneca. The protocol amendment must be signed by the investigator and approved by the regulatory authorities and IRB or IEC, if applicable, before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study as applicable in accordance with local requirements.

14.9 Use of Information and Publication

All information concerning MEDI7352, AstraZeneca operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by AstraZeneca or its designee to the investigator and not previously published, is considered confidential and remains the sole property of AstraZeneca. Case report forms also remain the property of AstraZeneca. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by AstraZeneca in connection with the continued development of MEDI7352 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of AstraZeneca. Publication or other public presentation of MEDI7352 data resulting from this study requires prior review and written approval of AstraZeneca. Publication policies will be specified in a separate document.

15 FINAL CLINICAL STUDY REPORT

AstraZeneca will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16 ETHICAL AND LEGAL CONSIDERATIONS

16.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the 2013 version of the Declaration of Helsinki, the applicable regulations of the countries in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

See Appendix D for regulation and guidelines.

16.2 Subject Information and Informed Consent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent prior to enrolment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent and/or assent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, AstraZeneca and/or the sponsor's designee. Collection of informed consent and/or assent has to be documented on the eCRF.

Furthermore, the subject will be informed that if he or she wishes to drop-out or withdraw at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be

reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3 Approval by Institutional Review Board or Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by the sponsor's representative before implementation.

16.4 Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

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18 ATTACHMENTS

18.1 Investigator's Agreement

PROTOCOL NUMBER:	D5680C00002
PROTOCOL TITLE:	A Randomised, Double-Blind, Placebo-Controlled, Dose-Response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Diabetic Neuropathy
AMENDED PROTOCOL:	13-Apr-2022

The undersigned acknowledges possession of and has read the Investigator's Brochure on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the amended study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of AstraZeneca.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to AstraZeneca within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with AstraZeneca and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance with the revised Declaration of Helsinki (2013) and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this amended protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Hy's Law Criteria
B. Contraception Guidance
C. Other Study-Specific Requirements
D. Regulations and Good Clinical Practice Guidelines

A. Hy's Law Criteria

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with AstraZeneca Neuroscience Innovative Medicines (NS iMed) clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational medicinal product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x upper limit of normal (ULN) and total bilirubin (TBL) ≥ 2 × ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases—eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to NS iMED medical monitoring and drug safety representatives).

The investigator will also remain vigilant for any local laboratory reports in which the identification criteria are met. Where this is the case, the investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results, the investigator will, without delay:

- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

FOLLOW-UP

Potential Hy's Law Criteria Not Met

If the subject does not meet PHL criteria, the investigator will:

- Inform the NS IMED representatives (medical monitoring and patient safety physicians) that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria Met

If the subject does meet PHL criteria, the investigator will:

- Notify the NS IMED representatives (medical monitoring and patient safety physicians), who will then inform the central study team

The medical monitor will contact the investigator, to provide guidance, discuss, and agree on an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact, the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations, as discussed with the study physician
- Complete the three liver CRF modules as information becomes available
- If at any time (in consultation with the study physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The

NS IMED physician and the NS IMED representative safety physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and, subsequently, a determination of whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the NS IMED standard reporting processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term, "Hy's Law") according to NS IMED standard processes.
- The "medically important" criterion for seriousness should be used if no other criteria for seriousness apply.
- As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term "Potential Hy's Law") applying criteria for seriousness and causality assessment as described above.
- Continue follow-up and review according to the agreed-on plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

REFERENCES

FDA Guidance for Industry (issued July 2009), *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

B. Contraception Guidance

For females:

Females without childbearing potential will be included in this study. Females without childbearing potential are defined as those who are surgically sterile (ie, women who have had a hysterectomy, bilateral ovariectomy (oophorectomy), bilateral salpingectomy, or bilateral tubal ligation) or those who are postmenopausal (defined as 12 months or more with no menses without an alternative medical cause).

For males:

Non-sterilized males who are sexually active with a female partner of childbearing potential must use condom and spermicide for the duration of the treatment period and for 3 months after the last administration of study drug. As male condom and spermicide are not considered to constitute a highly effective contraception method it is strongly recommended that female partners of a male study subjects also use a highly effective method of contraception throughout the study, including the protocol-specified follow-up period. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table B-1.

Table B-1: Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (UIS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) ◦ Oral (combined pill) ◦ Injectable ◦ Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [d] ◦ Injectable ◦ Implantable ◦ Intravaginal

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

C. Other Study-Specific Requirements

All scales and details of blood volumes for assessments will be provided in a study-specific manual.

D. Regulations and Good Clinical Practice Guidelines

1. Regulations

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

REASONS FOR AMENDMENT

1. Broadened ECG language to allow paper ECGs as an alternative to digital ECGs.
2. Clarified that the principal investigator's assessment of each ECG will be recorded in the eCRF as normal, abnormal and clinically significant, or abnormal and not clinically significant.

CCI

4. Clarified the details relating to the interim analysis after completion of stage 3.
5. Provided additional details of vital signs capture, particularly with regard to the use of a supine or sitting position.
6. Corrected typographical errors, capitalizations, and abbreviation definitions.

SUMMARY OF AMENDED SECTIONS

The changes being made in this version of the protocol are considered to be substantial.

Section 2.1 Synopsis

The synopsis was revised to incorporate the changes to the protocol that are described in this amendment.

Section 2.2 Schedule of Events

The Schedule of Events was revised to incorporate the changes to the protocol that are described in this amendment.

Section 4 LIST OF ABBREVIATIONS AND DEFINITIONS

The List of Abbreviations was revised to incorporate definitions for terms in the protocol that were not previously defined.

Section 5.2.4 Phase I Painful Osteoarthritis of the Knee Study

Text formerly read: In the ~~ongoing~~ Phase I study D5680C00004, 5 subjects had received blinded SC study treatment (MEDI7352 150 mg or placebo) as of 01 June 2021. Two of the of 5 treated subjects (40.0%) have had a total of 4 TEAEs as follows (1 subject each): dyspepsia, catheter site erythema, injection site pain, and paraesthesia.

Now reads: In the Phase I study D5680C00004, 5 subjects had received blinded SC study treatment (MEDI7352 150 mg or placebo) as of 01 June 2021. Two of the of 5 treated subjects (40.0%) have had a total of 4 TEAEs as follows (1 subject each): dyspepsia, catheter site erythema, injection site pain, and paraesthesia.

Section 6.3 Exploratory Objectives

Text formerly read:

Objectives	Endpoints
Secondary	
• To assess the safety and tolerability of MEDI7352 in subjects with PDN	• Safety and tolerability assessments: AEs and SAEs, physical and neurological examinations, neuropathy assessments (TNSn), strength (dorsiflexion) and deep tendon reflex (knee and ankle) assessments, vital signs, 12-lead ~~digital~~ ECGs ~~(with printouts)~~, clinical laboratory testing (haematology, clinical chemistry, coagulation, and urinalysis), motor and sensory nerve conduction, concomitant medication assessment, injection site reaction assessment, and infusion reaction assessments.

Now reads:

Objectives	Endpoints
Secondary	
• To assess the safety and tolerability of MEDI7352 in subjects with PDN	• Safety and tolerability assessments: AEs and SAEs, physical and neurological examinations, neuropathy assessments (TNSn), strength (dorsiflexion) and deep tendon reflex (knee and ankle) assessments, vital signs, 12-lead ECGs, clinical laboratory testing (haematology, clinical chemistry, coagulation, and urinalysis), motor and sensory nerve conduction, concomitant medication assessment, injection site reaction assessment, and infusion reaction assessments.

Section 7.1 Overall Study Design and Plan

Text formerly read: In stage 3 of the study, approximately 67 subjects will be randomly assigned to placebo or CCI of MEDI7352. The third stage will include an interim analysis to assess key assumptions of the sample size calculation. ~~**In stage 4 of the study, if there are no changes made following the interim analysis,**~~ eligible subjects will be randomly assigned to treatment with equal allocation across 3 dose levels of MEDI7352 or placebo to ensure approximately 236 subjects are evaluable for the efficacy analysis of stages 2 to 4 combined.

Now reads: In stage 3 of the study, approximately 67 subjects will be randomly assigned to placebo or CCI of MEDI7352. The third stage will include an interim analysis to assess key assumptions of the sample size calculation. **Upon enrolment of approximately 67 subjects in stage 3, approximately 165** eligible subjects will be randomly assigned to treatment with equal allocation across 3 dose levels of MEDI7352 or placebo to ensure approximately 236 subjects are evaluable for the efficacy analysis of stages 2 to 4 combined.

Section 7.2 Rationale and Discussion of Study Design

Text formerly read: The third stage will compare the highest expected efficacious dose, CCI, to placebo and an interim analysis that will ~~**enable**~~ decision making for stage 4 with respect to sample size ~~**re-estimation**~~ and dose allocation ratio.

Now reads: The third stage will compare the highest expected efficacious dose, CCI, to placebo and **includes** an interim analysis that will **confirm** decision making for stage 4 with respect to **exact** sample size and dose allocation ratio.

Section 7.3 Selection of Doses in the Study

Text formerly read: MEDI7352 ~~**is currently undergoing**~~ clinical evaluation for safety, PK, PD, and efficacy in a first-in-human study in subjects with painful OA of the knee (ClinicalTrials.gov Identifier:

NCT02508155). In that study, testing of single IV doses of up to CCI and repeat ascending IV doses of CCI ~~**and**~~ every 2 weeks have been completed. ~~**The final cohort comprising repeat IV doses of CCI is ongoing.**~~ Single SC doses of CCI have also been evaluated. ~~**To date,**~~ no safety or tolerability concerns ~~**have been**~~ reported. A full description of the current clinical experience with MEDI7352 is in Section 5.2.

Now reads:

MEDI7352 **has undergone** clinical evaluation for safety, PK, PD, and efficacy in a first-in-human study in subjects with painful OA of the knee (ClinicalTrials.gov Identifier: NCT02508155). In that study, testing of single IV doses of up to CCI and repeat ascending IV doses of CCI **and** CCI every 2 weeks have been completed. Single SC doses of CCI have also been evaluated. No safety or tolerability concerns **were** reported. A full description of the current clinical experience with MEDI7352 is in Section 5.2.

Section 10.1 Study Duration

Deleted:

~~**The overall study duration is expected to be 40 months (35 months of active screening and enrolment and 5 months of follow-up), but this may be extended depending on the requirements and recommendations of international and national public health authorities in relation to the coronavirus disease 2019 (COVID-19) pandemic.**~~

Section 10.2.1.1 Screening

Added:

11. Collect urine sample for the following:

- urinalysis
- urine drug screen
- urine pregnancy test (for women who are not surgically sterile) (If the screening urine pregnancy test is more than 7 days before the first day of treatment, it must be repeated prior to the first dose.)

CCI [redacted]

Section 10.2.2.1 Day 1 (Treatment 1)

Text formerly read:

4. Perform 3 replicates of 12-lead ~~d~~ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.

Now reads: 4. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.

Text formerly read: 11. Repeat 3 replicates of ~~d~~ECGs (with printouts) at 60 (±10) minutes after the start of IP administration, and 2 and 4 hours (±10 minutes) after the start of IP administration. Subjects must rest in the supine position for 10 minutes prior to each ECG recording session.

Now reads: 11. Repeat 3 replicates of ECGs (with printouts) at 60 (±10) minutes after the start of IP administration, and 2 and 4 hours (±10 minutes) after the start of IP administration. Subjects must rest in the supine position for 10 minutes prior to each ECG recording session.

Section 10.2.2.2 Days 14, 28, 42, 56, and 70 (Treatments 2 to 6)

Text formerly read: 5. Perform 3 replicates of 12-lead ~~d~~ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes (Days 28 and 56 only).

Now reads: 5. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes (Days 28 and 56 only).

Added: 8. Collect urine sample for the following:

- urinalysis

CCI

Section 10.2.2.5 Day 84 (End-of-Treatment; Week 12)

Text formerly read: 6. Perform 3 replicates of 12-lead ~~d~~ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.

Now reads: 6. Perform 3 replicates of 12-lead ECGs (with printouts) after the subject has been resting in the supine position for at least 10 minutes.

Added: 9. Collect urine sample for the following:

- urinalysis
- urine pregnancy test (for women who are not surgically sterile)

CCI

from all subjects who had a baseline sample collected at the screening visit.

Section 10.2.3 Follow-up (or Early Termination) Evaluation (Week 18)

Added: 8. Collect urine sample for the following:

- urinalysis
- urine pregnancy test (for women who are not surgically sterile)

CCI

Section 10.3.2.4 CCI

Text formerly read: CCI

Now reads:

Section 10.3.3.1.5 Vital Signs

Added: **Vital signs will be assessed as follows:**

- **Screening: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in supine position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.**
- **Day 1 pre-dose: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in supine position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.**
- **Day 1 post-dose: Supine and orthostatic BP and HR at 15 mins, 30 mins, 45 mins, 60 mins, 2 hours, and 4 hours after start of infusion. Temperature and supine and orthostatic BP**

and HR at 60 mins, 2 hours, and 4 hours after start of infusion. Respiratory rate at 15 mins, 60 mins, 2 hours, and 4 hours after start of infusion. The 60-minute assessments should be performed within 10 minutes of the end of the infusion. [Note: An acceptable window for these vital sign assessments is ± 5 mins in relation to the specified time].

- **Days 14, 28, 42, 56, and 70 pre-dose: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in sitting position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.**
- **Days 14, 28, 42, 56, and 70 post-dose: 5 minutes after completion of infusion, measure respiratory rate, temperature, and HR and BP after a 5-minute rest in sitting position. After measuring sitting vital signs, assess orthostatic BP and HR 1 minute after the subject stands.**
- **Days 71, 77, and Week 18 or early termination: Measure respiratory rate, temperature, and HR and BP after a 5-minute rest in sitting position. To assess orthostasis, repeat BP and HR 1 minute after the subject stands.**

Section 10.3.3.1.6 Twelve-lead Electrocardiogram

Text formerly read: ~~**The**~~ digital ECGs will be collected using the ECG equipment delivered by the central ECG laboratory (ECG lab) and will be transferred to and analysed by the ECG lab according to the lab's standard operating procedures. Further details are provided in the ECG Manual.

Paper printouts of the ~~**digital**~~ ECGs will be reviewed in real time by the principal investigator, or delegate, for safety monitoring. ~~**The following variables will be reported by the ECG Core laboratory: RR, PR/PQ, QRS, and QT intervals. Derived parameters (QTcF, HR, and others, as applicable) will be calculated by the statistician or designee.**~~

Now reads: **All subjects will undergo ECGs as indicated in the schedule of assessments. Where applicable,** digital ECGs will be collected using the ECG equipment delivered by the central ECG laboratory (ECG lab) and will be transferred to and analysed by the ECG lab according to the lab's standard operating procedures. Further details are provided in the ECG Manual.

Paper printouts of the **12-lead** ECGs will be reviewed in real time by the principal investigator, or delegate, for safety monitoring. **The results of the evaluation will be reported in the eCRF as *normal* or *abnormal* (if abnormal, the ECG is also to be reported as not clinically significant or clinically significant). The details of any ECG abnormalities should be described and captured in the eCRF (irrespective of whether they are considered not clinically significant or clinically significant).**

Section 13.1.6.4 Twelve-lead Electrocardiogram

Text formerly read: The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point. Abnormal results will be grouped as clinically significant and not clinically significant.

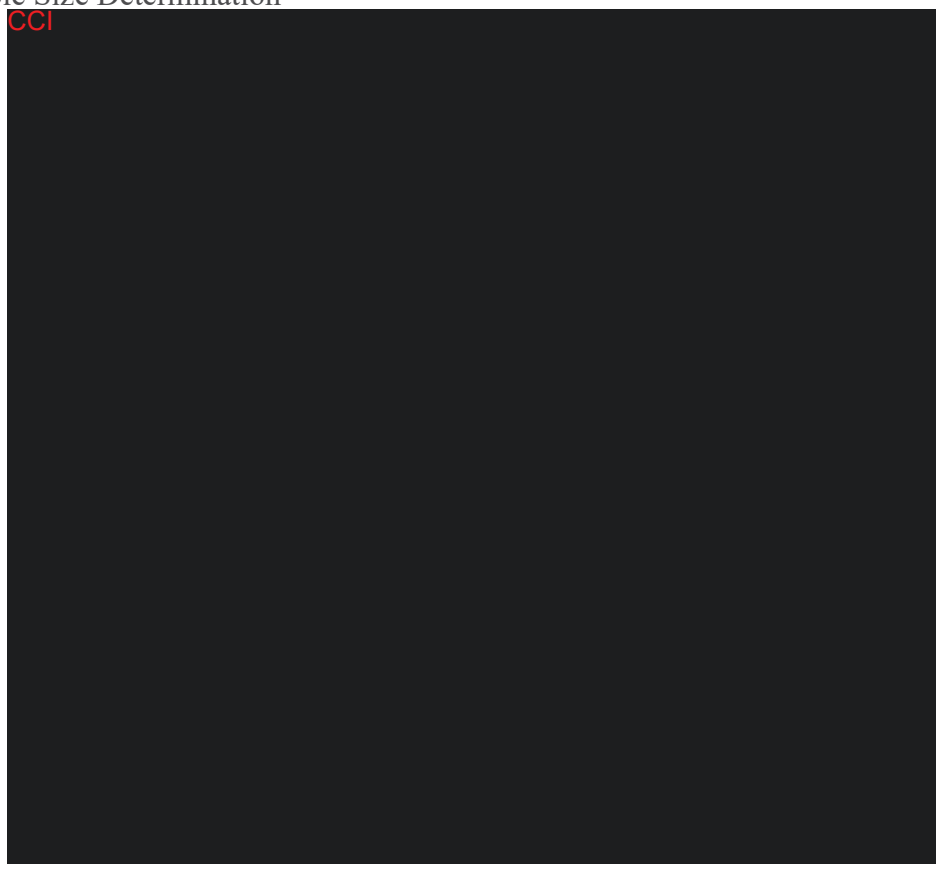
~~**If warranted, a comparison of QT results will be presented and descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR for each treatment group at each time point.**~~

Now reads: The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point. Abnormal results will be grouped as clinically significant and not clinically significant. **A description of ECGs evaluated as abnormal will be provided.**

If applicable (digital ECGs), descriptive summaries will be provided for measures provided by the ECG core laboratory from the digital ECGs for PR, QRS, QT, RR intervals and for the calculated variables QTcF and HR for each treatment group and time point.

Section 13.2 Sample Size Determination

Text formerly read: CCI



Now reads:

CCI

[redacted]

General

Minor typographical, abbreviation, and capitalization corrections were made throughout the protocol as necessary.