Clinical Study Protocol – Global Amendment 3	
Study Intervention	MEDI7352
Study Code	D5680C00003
Version	4.0
Date	28 June 2022

A Randomised, Double-blind, Placebo-controlled, Dose-response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

Sponsor Name: AstraZeneca AB

Regulatory Agency Identifier Number(s)

EudraCT number: 2020-003797-51

This Clinical Study Protocol Amendment has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D5680C00003

Amendment Number: 3

Investigational Product: MEDI7352

Study Phase: Phase IIb

Short Title: A Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	28-June-2022
Amendment 2	14-Oct-2021
Amendment 1	11-Mar-2021
Original Protocol (initial creation)	13-Aug-2020

Amendment 3 (28 June 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This global amendment 3 supersedes all global or country-specific protocol addendums dated prior to the date of this amendment as it incorporates the requirements detailed in these addendums.

Overall Rationale for the Amendment:

This protocol (study D5680C00003) has been amended to increase the study sample size to approximately 350 participants to maintain study power in light of a higher than anticipated rate of COVID-related withdrawals following randomisation. This amendment allows participants who have recovered from a previous COVID-19 infection to be enrolled sooner after full recovery from COVID-19 infection and allows for some participants to remain in the study after having had a COVID-19 infection. The amendment clarifies the interpretation of the prohibited concomitant medications from the start of the washout period until the Week 18 follow-up visit. In addition, the electrocardiogram visit windows are being extended to offer more flexibility for procedures at the site and prevent minor protocol deviations without affecting the integrity of the data. Minor text edits have been made as needed to increase clarity or correct the interpretation of the protocol.

The Protocol Amendment Summary of Changes Table for this global amendment 3 is presented in Appendix M.

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3
TABLE OF CONTENTS 4
LIST OF FIGURES 7
LIST OF TABLES 8
1 PROTOCOL SUMMARY 10
1.1 Synopsis 10
1.2 Schema 17
1.3 Schedule of Assessments 18
2 INTRODUCTION 27
2.1 Study Rationale 27
2.2 Background 27
2.2.1 Clinical Experience with anti-NGF and anti-TNF Therapeutics 28
2.2.2 Clinical Experience with MEDI7352 29
2.3 Benefit/Risk Assessment 31
2.3.1 Risk Assessment 31
2.3.1.1 Potential Risks Based on Mechanisms of Action 32
2.3.1.2 Potential Risks Based on Class Effects 34
2.3.1.3 Considerations for Route of Administration 34
2.3.1.4 General Risk-Mitigation Plan 34
2.3.2 Benefit Assessment 36
2.3.3 Overall Benefit/Risk Summary 37
2.3.4 Overall Benefit/Risk Conclusion 37
3 OBJECTIVES AND ENDPOINTS 39
4 STUDY DESIGN 43
4.1 Overall Design 43
4.1.1 Study Conduct Mitigation During Study Disruptions due to Cases of Public Health Crisis 45
4.1.2 Additional Risk-Mitigation Procedures Implemented in the Context of the SARS-CoV-2/COVID-19 Pandemic 46
4.2 Scientific Rationale for Study Design 48
4.3 Justification for Dose 49
4.4 End-of-Study Definition 50
5 STUDY POPULATION 50
5.1 Inclusion Criteria 50
5.2 Exclusion Criteria 52
5.3 Lifestyle and Activity Considerations 57

5.3.1 Meals and Dietary Restrictions 58
5.3.2 Tobacco Restrictions 58
5.3.3 Other Restrictions 58
5.4 Screen Failures 58
5.4.1 Rescreening 59
6 STUDY INTERVENTION 59
6.1 Study Intervention(s) Administered 59
6.1.1 Investigational Products 59
6.2 Preparation/Handling/Storage/Accountability 61
6.2.1 Preparation and Administration of Subcutaneous Injections 61
6.2.2 Handling, Labelling, and Storage 63
6.2.3 Accountability 63
6.3 Measures to Minimise Bias: Randomisation and Blinding 64
6.3.1 Methods for Unblinding 64
6.4 Study Intervention Compliance 65
6.5 Concomitant Therapy 65
6.5.1 Permitted Concomitant Therapy 66
6.5.2 Prohibited Concomitant Medications 67
6.5.3 Rescue Medication 68
6.6 Dose Modification 69
6.7 Intervention after the End of the Study 69
7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL 69
7.1 Discontinuation of Investigational Product 69
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product 70
7.1.2 Procedures for Early Discontinuation of Investigational Product 72
7.1.3 Temporary Discontinuation of Investigational Product 73
7.1.4 Procedures for Handling Incorrectly Enrolled or Randomised Subjects 75
7.2 Subject Withdrawal from the Study 75
7.3 Lost to Follow-up 76
8 STUDY ASSESSMENTS AND PROCEDURES 77
8.1 Efficacy/Pharmacodynamics Assessments 81
8.1.1 Daily Pain Scores 81
8.1.2 Patient Global Assessment of Osteoarthritis 81
8.1.3 Western Ontario and McMaster Universities Osteoarthritis Index 81
8.1.4 Daily Sleep Interference Scale 82
8.1.5 36-Item Short Form Health Survey Questionnaire (acute recall) 82
8.1.6 European Quality of Life-5 Dimensions (EQ-5D-5L) 83
8.1.7 WPAI:OA questionnaire 84
8.1.8 Assessment of Healthcare Resource Utilisation 84
8.1.9 Rescue Medication 85
8.2 Safety Assessments 86

8.2.1 Physical Examinations 86
8.2.2 Neurological Examinations 86
8.2.3 Vital Signs 87
8.2.3.1 Blood Pressure and Pulse Rate 87
8.2.3.2 Orthostatic Blood Pressure Measurements and Follow-up of Confirmed Orthostatic Hypotension 88
8.2.3.3 Blood Pressure Measured by an Ambulatory Blood Pressure Monitoring Device 89
8.2.3.4 Body Temperature 90
8.2.3.5 Respiratory Rate 90
8.2.4 Electrocardiograms 90
8.2.5 Survey of Autonomic Symptoms (SAS) 91
8.2.6 Imaging 91
8.2.6.1 Radiographic (X-ray) Assessment 91
8.2.6.2 Magnetic Resonance Imaging 92
8.2.7 Follow-up of Clinically Significant Findings in Major Joints 93
8.2.8 Total Neuropathy Scores-Nurse 94
8.2.9 Injection Site Reactions 94
8.2.10 Procedures for Subjects Undergoing Joint Replacement 95
8.2.11 Clinical Safety Laboratory Assessments 95
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests 97
8.2.11.2 Pregnancy 100
8.2.11.3 Urine Drug Screen 101
8.3 Adverse Events and Serious Adverse Events 101
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 101
8.3.2 Follow-up of AEs and SAEs 102
8.3.3 Adverse Event Data Collection 102
8.3.4 Causality Collection 103
8.3.5 Adverse Events of Special Interest 103
8.3.6 Adverse Events Based on Signs and Symptoms 104
8.3.7 Adverse Events Based on Examinations and Tests 104
8.3.8 Hy's Law 104
8.3.9 Reporting of Serious Adverse Events 105
8.3.10 Pregnancy 105
8.3.10.1 Maternal Exposure 106
8.3.10.2 Paternal Exposure 107
8.3.11 Medication Error 107
8.3.12 Management of investigational product-related toxicities 107
8.4 Overdose 108
8.5 Human Biological Samples 109
8.5.1 Pharmacokinetics 109
8.5.1.1 Determination of Drug Concentration 110
8.5.2 Immunogenicity Assessments 110
8.5.3 Pharmacodynamics 111
8.6 CCI
8.6.1 CCI

8.6.1.1 Pharmacodynamic Biomarkers 111
8.6.1.2 CCI
8.6.1.3 CCI
8.6.1.4 CCI
8.6.2 Other Study-related Biomarker Research 113
8.7 Optional Genomics Initiative Sample 113
8.8 Medical Resource Utilisation and Health Economics 114
9 STATISTICAL CONSIDERATIONS 114
9.1 Statistical Hypotheses 114
9.2 Sample Size Determination 115
9.3 Populations for Analyses 115
9.4 Statistical Analyses 116
9.4.1 General Considerations 116
9.4.2 Efficacy 116
9.4.2.1 Primary Endpoint 117
9.4.2.2 Secondary Endpoint(s) 118
9.4.2.3 CCI
9.4.3 Safety Analyses 119
9.4.3.1 Adverse events 119
9.4.3.2 Clinical Laboratory Evaluations 120
9.4.3.3 Vital Signs 120
9.4.3.4 12-Lead Electrocardiogram 120
9.4.3.5 Physical and Neurological Examination Findings 121
9.4.3.6 Other Safety Endpoint(s) 121
9.4.4 Other Analyses 121
9.4.4.1 Pharmacokinetics 121
9.4.4.2 Pharmacodynamics 121
9.4.4.3 Pharmacogenetics 121
9.4.4.4 CCI
9.4.4.5 Immunogenicity 122
9.4.5 CCI
9.4.6 Sensitivity Analysis 122
9.5 Interim Analyses 122
9.6 Data Monitoring Committees 122
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 123
11 REFERENCES 248

LIST OF FIGURES

Figure 1 Study Design 17

LIST OF TABLES

Table 1 Schedule of Activities 18
Table 2 Primary and Secondary Objectives 39
Table 3 Investigational Products in Study D5680C00003 60
Table 4 CCI
Table 5 Threshold values for the SF-36v2 scale and summary measures 83
Table 6 Orthostatic Blood Pressure Criteria and Management 88
Table 7 Local Reaction to Injectable Product 94
Table 8 Required Investigations and Management of Cases of Abnormal Liver Function 98
Table 9 Populations for Analysis 115
Table F10 Lab Kit for Central Laboratories for Investigations and Management of Cases of Abnormal Liver Function (including Hy's Law cases) 154
Table I11 Imaging Assessments to be Performed During the Study 161
Table I12 Schedule of Assessments - Imaging 162
Table J13 Highly Effective Methods of Contraception 163
Table K14 Half-lives of NSAIDs and Other Analgesics 164

LIST OF APPENDICES

Appendix A Clinical Study Protocol Signatures 124
Appendix B Regulatory, Ethical, and Study Oversight Considerations 131
Appendix C Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting 138
Appendix D Handling of Human Biological Samples 143
Appendix E Optional Genomics Initiative Sample 145
Appendix F Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 149
Appendix G Anaphylaxis: Definition, Signs, Symptoms, and Management 156
Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis 159
Appendix I Summary of Imaging Assessments 161
Appendix J Contraception Guidance 163
Appendix K Half-lives of Nonsteroidal Anti-inflammatory Drugs and Other Analgesics 164

Appendix L Abbreviations 166
Appendix M Protocol Amendment History..... 170

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomised, Double-blind, Placebo-controlled, Dose-response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

Short Title: A Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

Rationale

MEDI7352 is being developed for the treatment of chronic pain. This randomised, double-blind, placebo-controlled study is designed to evaluate the safety and efficacy of CCI MEDI7352 in participants with painful osteoarthritis (OA) of the knee. Placebo is included in the study to permit comparative assessment of the safety, tolerability, and efficacy of MEDI7352 and to evaluate the benefit/risk balance of MEDI7352. This Phase IIb dose-response study will assess the efficacy and safety of multiple doses of MEDI7352 compared to placebo administered CCI in participants with painful OA of the knee, prior to advancing MEDI7352 into larger clinical studies of longer duration.

Objectives and Endpoints

The primary and secondary objectives and associated endpoints are detailed below. For tertiary/exploratory objectives and endpoints, see Section 3 of this protocol.

Objectives	Estimands descriptions/endpoints
Primary objectives	
To assess the efficacy of MEDI7352 compared to placebo on chronic pain in participants with painful OA of the knee at Week 12	• Population: Adults with moderate-to-severe chronic OA pain of the knee, persistent for 3 months or longer, not adequately controlled by standard-of-care treatments • Primary endpoint: ! Change in the weekly average of daily NRS pain scores from baseline to Week 12 • Intercurrent events: ! Discontinuation due to lack of efficacy or an AE ! Discontinuation due to other reasons such as loss to follow-up or external circumstances ! Taking prohibited pain medication during the treatment period ! Taking excessive permitted rescue medication • Summary measures: ! Difference in mean changes in the weekly average of daily NRS pain scores between MEDI7352 doses and placebo

Objectives	Estimands descriptions/endpoints
	! An 'attributable' estimand strategy will be adopted for data missing or affected by any of the above intercurrent events: missing or affected primary endpoint values will be imputed, but the method of imputation will differ depending upon the intercurrent event. Specifically, data missing due to discontinuation due to lack of efficacy or an AE will be imputed assuming an unfavourable outcome. Similarly, data affected by prohibited or excessive rescue medication will be set to missing and imputed assuming an unfavourable outcome.
Secondary objectives	
To assess the efficacy of MEDI7352 compared to placebo on additional measures of efficacy in participants with painful OA of the knee	Key secondary endpoints: • Change in the WOMAC pain subscale from baseline to Week 12 • Change in the WOMAC physical function subscale from baseline to Week 12 • Change in the PGA of OA from baseline to Week 12 Other secondary endpoints: • Change in the WOMAC pain subscale from baseline to Weeks 2, 4, 6, 8, 10, and 18 • Change in the WOMAC physical function subscale from baseline to Weeks 2, 4, 6, 8, 10, and 18 • Change in the WOMAC overall scores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 18 • Change in the WOMAC stiffness scores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 18 • Change in PGA of OA from baseline to Weeks 2, 4, 8, 10, and 18 • Percentage of responders as measured by the OARSI responder index using the OMERACT-OARSI definition (Pham et al 2004) at Weeks 2, 4, 8, 12, and 18 • Percentage of participants who have achieved an improvement of ≥ 2 points in PGA of OA at Weeks 2, 4, 8, 12, and 18 • Change in the weekly average of daily NRS pain scores from baseline to Weeks 2, 4, 6, 8, 10, and 18 • Percentage of participants who have achieved ≥ 30% and ≥ 50% reductions in the weekly average of daily NRS pain scores from baseline to Weeks 2, 4, 8, 12, and 18 • Percentage of participants who have achieved ≥ 30% and ≥ 50% reductions in WOMAC pain subscale scores at Weeks 2, 4, 8, 12, and 18 • Percentage of participants who have achieved ≥ 30% and ≥ 50% reductions in WOMAC physical function subscale at Weeks 2, 4, 8, 12, and 18
To assess the PK of MEDI7352 in participants with painful OA of the knee	• Serum concentration of MEDI7352

Objectives	Estimands descriptions/endpoints
To assess immunogenicity of MEDI7352 in participants with painful OA of the knee	• Presence of ADA to MEDI7352 • ADA titre
Safety objectives	
To assess the safety and tolerability of MEDI7352 compared with placebo in participants with painful OA of the knee	Safety and tolerability will be evaluated based on AEs, vital signs, and clinical laboratory assessments, including but not limited to: • AEs and SAEs • Physical examinations • Neurological examinations • Total Neuropathy Score-nurse • Weight • Vital signs (supine and orthostatic BP, pulse rate, temperature, respiratory rate) • Survey of Autonomic Symptoms • 12-lead ECGs • Clinical laboratory testing (haematology, chemistry, coagulation, and urinalysis) • CRP (inflammatory biomarker) • Concomitant medications and therapies • Injection site reactions • X-ray or/and MRI of large joints [a]

[a] Detailed information about the joints to be evaluated by X-ray and/or MRI is found in Section 8.2.6 and Appendix I.

ADAs, antidrug antibodies; AE(s), adverse event(s); BP, blood pressure, CRP, C-reactive protein; ECGs, electrocardiograms; MRI, magnetic resonance imaging; NRS, numerical rating scale; OA, osteoarthritis; OMERACT-OARSI, Outcome Measures in Rheumatology-Osteoarthritis Research Society International; PGA, Patient's Global Assessment; PK, pharmacokinetics; SAEs, serious adverse events; WOMAC, Western Ontario and McMaster Universities Osteoarthritis

Overall Design

This is a Phase IIb, multinational, multicentre, randomised, double-blind, placebo-controlled, dose-response study of MEDI7352 in participants 18 to 80 years of age (inclusive) with moderate-to-severe chronic pain of the knee during the previous 3 months or longer, caused by OA, and not adequately controlled by standard-of-care treatments. The study consists of a screening period of up to 45 days, a 12-week treatment period, and a 24-week follow-up (FU) period (Table 1).

Daily pain scores (as measured on an 11-point numerical rating scale [NRS]) recorded at the first screening visit and from Day -7 to Day -1 (inclusive) will be used be used to determine eligibility. In addition, X-ray features in the target knee joint should be consistent with at least Grade 2 OA on the Kellgren and Lawrence grading scale of 0 to 4 as per central reader evaluation.

On Day 1, participants will be randomised (after confirming eligibility criteria) to one of 4 doses of MEDI7352 ([redacted]) or placebo. The investigational products (IPs) will be administered [redacted] every 2 weeks (Q2W). Each participant will receive 6 doses of MEDI7352 or placebo during the treatment period.

After the end-of-treatment (EOT) visit at Week 12, participants will enter the FU period, which comprises 3 clinic visits (Weeks 18, 32, and 36) and 4 FU phone calls (Weeks 15, 21, 24, and 28). All participants who receive IP are expected to complete the FU period.

Interim Analysis

The study incorporates 2 interim analyses: (1) a futility analysis will take place when approximately 25% of participants are evaluable for the primary endpoint; this analysis will assess the likely success of the study outcome and will enable the sponsor to make a go/no-go decision regarding continuation of the study; and (2) an interim analysis of efficacy data will take place when approximately 50% of participants are evaluable for the primary endpoint; this analysis will enable the sponsor to plan future project-related activities, but without making any changes to the current study.

No alpha adjustment is required for the interim analyses because early stopping for efficacy is not a feature of the study design.

Disclosure Statement

This is a Phase IIb, randomised, parallel-group, placebo-controlled, double-blind treatment study of MEDI7352 with 5 cohorts that are participant- and investigator-blinded.

Number of Subjects

This is a multinational, multicentre, interventional study in which approximately 350 eligible participants will be randomly assigned to the IPs (one of 4 dose levels of MEDI7352 or placebo).

Intervention Groups and Duration

Screening period: up to 45 days

Randomisation: participants will be randomised in a ratio of 1:1:1:1:1, respectively, to one of the following 5 treatment cohorts:

- Cohort 1: [redacted] MEDI7352 Q2W administered [redacted]
- Cohort 2: [redacted] MEDI7352 Q2W administered [redacted]
- Cohort 3: [redacted] MEDI7352 Q2W administered [redacted]
- Cohort 4: [redacted] MEDI7352 Q2W administered [redacted]
- Cohort 5: Placebo to match MEDI7352 Q2W administered [redacted]

Treatment period: 12 weeks with 6 fixed doses of IP administered at Weeks 0 (Day 1), 2, 4, 6, 8, and 10 and an EOT visit conducted at Week 12

FU period: 24-week FU period with a final FU visit at Week 36 (± 7 days)

The maximum study duration for each participant is approximately 50 weeks. The overall study duration is expected to be 31 months (18 months of active screening and enrolment, 11 months of treatment and FU, and 2 months for database lock).

Data Monitoring Committees:

- Data and Safety Monitoring Board (DSMB): The DSMB will conduct periodic reviews of safety data from all enrolled participants throughout the clinical study. The DSMB will make recommendations to the sponsor, based on these data, on the future conduct of the clinical study and in particular on whether to continue, terminate, or modify the clinical study.
- Independent Efficacy Review Group: This group will be independent of the study team and will review, interpret, and make decisions on future conduct of the clinical study based on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes.
- Rapidly Progressive Osteoarthritis (RPOA) Adjudication Committee (RPOA-AC): The role of this committee is to independently review, interpret, and adjudicate possible or probable joint safety events including but not limited to RPOA, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture cases that are experienced by the study participants. The RPOA-AC will review and adjudicate all treatment-emergent joint safety events that meet SAE or severe AE criteria or which led to joint replacement or other arthroplasty procedures.

Statistical Methods

An ‘attributable’ estimand strategy will be adopted for primary endpoint data missing or affected by any of the following 4 intercurrent events:

- Discontinuation due to lack of efficacy or an adverse event
- Discontinuation due to other reasons such as loss to FU or external circumstances
- Taking prohibited pain medication during the treatment period
- Taking excessive permitted rescue medication

Missing or affected primary endpoint values will be imputed, but the method of imputation will differ depending upon the intercurrent event.

Analysis Populations

- Screening set: This set includes all participants who provide informed consent and/or assent and provide demographic and/or baseline screening assessments, regardless of the participant's randomisation and treatment status in the study.
- Full analysis set: This set will be used for all efficacy analyses, and it is defined according to the intent-to-treat principle as including all randomised participants.
- Pharmacokinetics (PK) set: This set includes all participants who received at least one dose of double-blind IP per the protocol for whom any postbaseline PK data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses.
- Safety analysis set: This set will include all participants who receive at least one dose of double-blind IP.

Sample Size Determination

Approximately 350 eligible participants will be randomly assigned to IPs (MEDI7352 or placebo). Recruitment will continue until the planned power of the study is achieved (ie, when statistical information equivalent to 255 participants completing the treatment period is reached) or approximately 350 randomised participants, whichever is sooner. The statistical information will be calculated based upon ongoing blinded study data. Further details will be given in the Statistical Analysis Plan.

With statistical information equivalent to 255 evaluable participants, the study will have greater than 90% power to detect a statistically significant (at overall 1-sided $\alpha = 0.025$) dose-response relationship using a multiple comparison procedure-modelling (MCP-Mod) approach for the primary endpoint 'Change in the weekly average of daily NRS pain scores from baseline to Week 12'. This assumes that the true Week 12 placebo-corrected change from baseline difference at the [redacted] dose is 1.5, and the true dose-response follows a maximum response (Emax) relationship with a dose that produces half of the Emax (ED50) = [redacted] and a standard deviation (SD) = 2.4.

Subject Characteristics and Disposition

Baseline participant characteristics will be listed and included in summaries as appropriate. Investigational product administration will be summarised in terms of each participant's total dose and number of [redacted] administrations received using descriptive statistics.

Efficacy Analyses

All efficacy variables will be summarised 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 the 'last-observation-carried-forward' or 'baseline-observation-carried-forward', as appropriate.

The main statistical analysis of the primary efficacy endpoint at Week 12 will use a MCP-Mod approach, which is a well-established statistical methodology for establishing both the existence of a dose response and modelling of the underlying dose-response relationship. Both the European Medicines Agency (EMA 2013) and the Food and Drug Administration (FDA) (FDA 2015) have recognised MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose-finding studies under model uncertainty. The significance level of the analysis will be at 1-sided $\alpha = 0.025$. A multiple imputation approach will be used for missing or unevaluable data. The method of imputing missing values will be dependent on the reasons for missing or unevaluable data.

Pairwise testing of prespecified MEDI7352 doses versus placebo of the primary and key secondary endpoints will be performed using a sequentially rejective multiple comparison approach (or similar) to ensure overall family-wise type 1 error across primary and key secondary endpoints is controlled at 1-sided $\alpha = 0.025$ (Bretz et al 2009).

Clinical Pharmacology Analyses

PK: PK of MEDI7352 will be characterised with a population PK model. MEDI7352 trough concentration (C_{trough}) will be summarised descriptively.

Pharmacodynamics (PD) and biomarkers: PD variables (free and/or total nerve growth factor, CXCL13, and other relevant biomarkers) will be summarised using descriptive statistics. Biomarker results will be listed. The association between PD variables and efficacy endpoints will be evaluated.

Immunogenicity: A summary of the number and percentage of participants who developed detectable antidrug antibodies (ADA) to MEDI7352 as well as ADA titres in all cohorts will be presented. Immunogenicity results will be listed. The effect of ADA on PK, PD, safety, and efficacy will be evaluated.

Analysis of pharmacogenetics data will be described in a separate analysis plan.

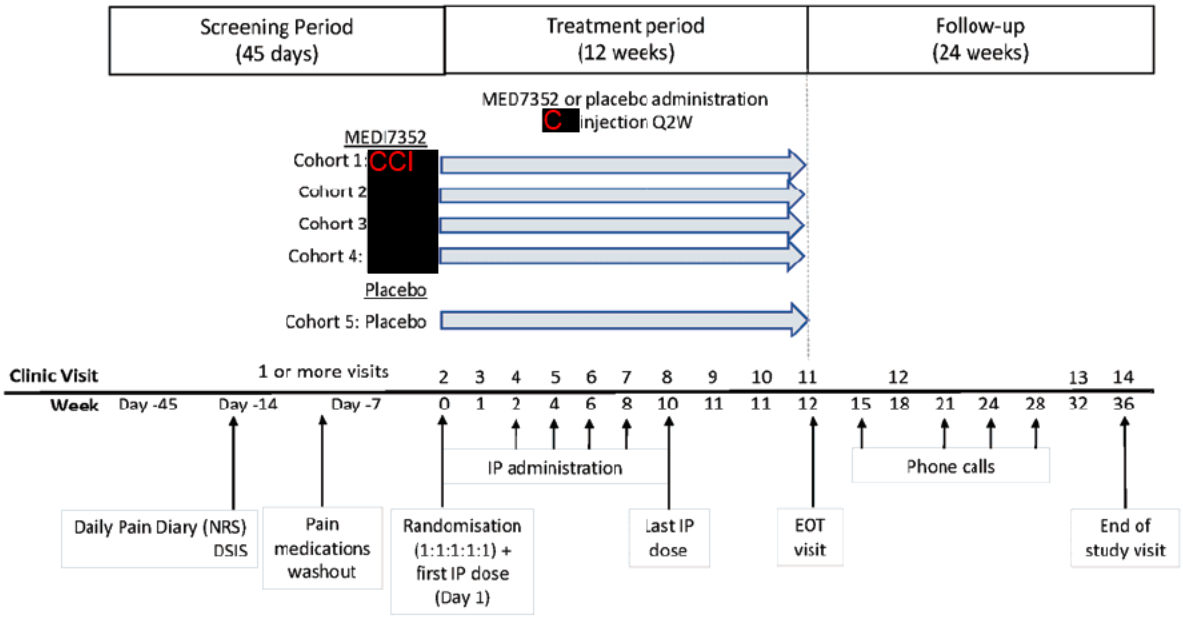
Safety Analyses

Safety and tolerability data will be summarised descriptively by using tables, listings, and graphs, as appropriate.

1.2 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design



The screening period is up to 45 days; one rescreening attempt is allowed (Section 5.4.1).

Pain medication washout is at least 48 hours or 5 half-lives, whichever is longer, prior to the start of the NRS pain score baseline period on Day -7.

The baseline NRS pain score period comprises the scores from Day -7 to Day -1 (inclusive).

Visit 3 (Day 7), Visit 9 (Day 74) and Visit 10 (Day 77) may be performed at the participant's home by a qualified health care provider.

DSIS, daily sleep interference scores; EOT, end of treatment; IP, investigational product; NRS, numerical rating scale; Q2W, every 2 weeks; CCI

1.3 Schedule of Assessments

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
General procedures																
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Height and weight (BMI)	X										X [g]					
Demographics and medical history	X															
X-ray for knees, hips, and shoulders [h]	X														X	
MRI of bilateral knees and joints with a KL grade at baseline of ≥ 3 [i]	X															
Concomitant medications and therapies [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
Start washout of any current pain medications including NSAIDs, COX-2 inhibitors, and other prohibited pain medications [a]	X															
Randomisation [k]		X														
IP administration CCI		X		X	X	X	X	X								
Efficacy assessments																
Screening pain intensity score [l]	X															
Training and reminders on rating pain and entering ratings on ePRO system	Day -14 [a]	X		X	X	X	X	X			X					
Daily pain diary (NRS) [m]	Day -14 →															
DSIS diary [m]	Day -14 →															

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
WOMAC (pain, stiffness, and function subscales) [n]		X		X	X	X	X	X			X [e]		X			
PGA [n]		X		X	X	X	X	X			X [e]		X			
CCI [redacted]																
Safety assessments																
Physical and neurological examination	X	X		X	X	X	X	X			X		X		X	X
12-lead ECG [o]	X	X		X	X		X	X			X				X	
24-hour ABPM [p]	Day -14 [a]							X								
Total neuropathy score-nurse	X	X		X	X	X	X	X			X				X	
Survey of autonomic symptoms		X														X

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
Vital signs (BP and pulse rate [supine], respiratory rate, and body temperature) [q]	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Orthostatic BP [r]	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Injection site assessment [s]		X		X	X	X	X	X								
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments																
Urine collection for:																
Drug screen	X [a]			X												
Urinalysis	X	X		X	X	X	X	X			X				X	
Pregnancy tests [t]		X		X	X	X	X	X								X
CCI																
Blood collection for:																
Haematology, chemistry, and coagulation [v]	X	X		X	X	X	X	X			X				X	

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
Serology (HIV, hepatitis B, hepatitis C, and tuberculosis [QuantiFERON])	X															
Serum pregnancy test	X [a]															
Haemoglobin A_1c	X														X	
ACPA antibodies	X															
FSH test screening for women < 50 years	X															
Immunogenicity (ADA) sampling		X [w]	X	X [w]	X [w]	X [w]	X [w]	X [w]	X	X	X [x]		X		X	
PK analysis		X [w]	X	X [w]	X [w]	X [w]	X [w]	X [w]	X	X	X [x]		X		X	
PD and exploratory biomarkers:																
PD: free NGF		X [w]	X	X [w]	X [w]	X [w]	X [w]	X [w]	X	X	X [x]		X		X	
PD: total NGF		X [w]	X	X [w]	X [w]	X [w]	X [w]	X [w]	X	X	X [x]		X		X	
PD: CXCL13		X [w]	X	X [w]	X [w]	X [w]	X [w]	X [w]	X	X	X [x]		X		X	

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
CCI [redacted]																
Other assessments																
Dispense rescue medicine [z]	X	X	X	X	X	X	X	X		X	X					
Record rescue medication use [z]	Day -14 →															
Return rescue medication/check compliance [aa]		X	X	X	X	X	X	X	X	X	X		X			
Start standard-of-care treatment [bb]													X			
COVID-19 symptom screening [cc]		X		X	X	X	X	X								

Table 1 Schedule of Activities

		Double-blind treatment period (12 weeks)										Follow-up period [b] (24 weeks)				
Study week	**Screening/ baseline [a]**	**Wk 0 [c]**	**Wk 1 ± 3 d [d]**	**Wk 2 ± 3 d**	**Wk 4 ± 3 d**	**Wk 6 ± 3 d**	**Wk 8 ± 3 d**	**Wk 10 ± 3 d**	**Wk11 ± 3 d [d]**	**Wk 11 ± 3 d [d]**	**(EOT or ET [e]) Wk 12 ± 3 d**	**Wk 15 ± 3 d**	**Wk 18 ± 7 d**	**Wk 21, 24, & 28 ± 3 d**	**Wk 32 ± 7 d**	**Wk 36 ± 7 d**
Study day	**Day -45 to -1**	**D 1**	**D 7**	**D 14**	**D 28**	**D 42**	**D 56**	**D 70**	**D 74**	**D 77**	**D 84**	**D 105**	**D 126**	**D 147, 168, & 196**	**D 224**	**Day 252**
Clinic visit (V)	**V1**	**V2**	**V3**	**V4 [f]**	**V5 [f]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Phone call 1**	**V12**	**Phone calls 2, 3, & 4**	**V13**	**V14**
COVID-19 nose and/or throat/saliva swab (SARS-CoV-2-test) [cc, dd]		X		X	X	X	X	X								
CCI																

[b] For participants who discontinued IP early, the 3 FU clinic visits and 4 phone calls will occur at the times indicated below (Section 7.1.2):

- FU visit 1: Corresponds to Week 18; to be performed 8 weeks after the last IP administration
- FU visit 2: Corresponds to Week 32; to be performed 22 weeks after the last IP administration
- FU visit 3: Corresponds to Week 36; to be performed 26 weeks after the last IP administration
- FU phone calls 1, 2, 3, and 4: Corresponds to Weeks 15, 21, 24, and 28, respectively; to be conducted 5, 11, 14, and 18 weeks after the last IP administration, respectively

[c] For additional information on timing of assessments to be performed on Day 1 (ie, before randomisation, after randomisation/prior to IP administration, and after IP administration), see Section 8 "Double-blind Treatment Period".

[d] Visit 3 (Day 7), Visit 9 (Day 74), and Visit 10 (Day 77) may be performed at the participant's home by a qualified health care provider. Visit 9 (D 74) and Visit 10 (D 77) cannot be on the same day.

[e] The Week 12 visit is the EOT visit for participants who complete the treatment period. For participants who discontinue IP early, the Week 12 visit is the ET visit. Participants who discontinue IP early will be asked to complete the assessments at the ET visit (Week 12 assessments) as soon as possible after IP discontinuation; no efficacy assessments will be conducted beyond the ET visit (Section 7.1.2).

[f] On study Visit 4 (Day 14) and Visit 5 (Day 28), study participants will remain under observation for at least 2 hours after IP administration.

[g] Only weight will be measured at the Week 12/ET visit (Section 8.2.1).

[h] If other major joints (elbows, wrists, and ankles) exhibit signs or symptoms associated with OA, these should also be imaged during screening. At the Week 32 follow-up visit, safety X-ray imaging will be performed on knee and hip joints only. Unscheduled X-ray should be done "for cause" for any joints other than hip joints with a KL grade at baseline of ≥ 3, for which MRI would be required as a first step of the assessment of joint safety event (Section 8.2.6.1 and Section 8.2.7).

[i] An MRI of the bilateral knee joints and the joints with a KL grade at baseline of ≥ 3 must be done during the screening period. Unscheduled MRIs should be done "for cause" on the knee joints or the joints with a KL grade at baseline of ≥ 3 to follow up on any newly occurring symptoms or worsening of symptoms considered clinically significant by the investigator (Section 8.2.6.2 and Section 8.2.7).

[j] Concomitant medications/therapies will be recorded from the first screening visit and will continue to be recorded at each visit throughout the treatment and follow-up periods (Section 6.5).

[k] If necessary, the randomisation transaction via IRT/RTSM can be performed on Day -1.

[l] Participants must have a self-reported pain intensity score in the target joint ≥ 5 (as assessed by an 11-point NRS) during the week prior to the first screening visit.

[m] Once ePRO training is completed, participants will record daily NRS pain (Section 8.1.1) and DSIS scores (Section 8.1.4) from Day -14 until the FU visit at Week 18. Participants who discontinue IP early will stop recording daily NRS pain and DSIS scores after the ET visit. The average of daily NRS pain scores from Day -7 to Day -1 (inclusive) will also be used to determine eligibility.

[n] On dosing days, the WOMAC (Section 8.1.3) and PGA of OA (Section 8.1.2) questionnaires will be completed prior to IP administration.

[o] On Day 1, ECG recording will be performed 30 to 120 minutes prior to IP administration (and prior to randomisation) and 4 hours ± 30 minutes after IP administration; 30 to 120 minutes prior to IP administration at Weeks 2, 4, 8, and 10; and thereafter at Week 12 and Week 32. ECG should be performed prior to any blood draw (Section 8.2.4).

CCI

[q] Supine BP/pulse rate (Section 8.2.3.1), respiratory rate (Section 8.2.3.5), and body temperature (Section 8.2.3.4) will be taken at all clinic visits. On all dosing days, vital signs (supine BP, pulse rate, respiratory rate, and body temperature) are to be assessed prior to any blood draw and IP administration (and prior to randomisation on Day 1) and repeated 5 ± 5 minutes after completion of IP administration. On Day 1, vital signs are also to be assessed at the following time points:

- Supine BP/pulse rate: at 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration
- Body temperature: at 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration
- Respiratory rate: at 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration

[r] Orthostatic BP will be measured at all clinic visits prior to any blood draw and IP administration (and prior to randomisation on Day 1), where applicable. Orthostatic BP will be measured 1 and 3 minutes after the participant stands (Section 8.2.3.2).

[s] On Day 1, injection site reactions will be monitored at approximately 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after completion of IP administration. On the remaining dosing days, injection site reactions will be monitored per standard process of AE collection (participants will be instructed to report any changes that occurred at the injection site) (Section 8.2.9).

[t] A urine pregnancy test (applicable for women who are not surgically sterile) should be performed and the results assessed at all dosing visits prior to IP administration and at the Week 36 visit. The results must be negative in order to proceed with IP administration (Section 8.2.11.2).

CCI

[v] Abnormal haematology, chemistry, or coagulation tests could be repeated once for confirmation (Section 8.2.11).

CCI

[z] Participants who develop unacceptable pain (including the washout period) will be permitted to initiate rescue therapy with paracetamol. Study sites will provide the rescue medication at the indicated visits. Rescue medication will be recorded daily from Day -14 until the FU visit at Week 18. Participants who discontinue IP early, will stop recording rescue medication after the ET visit (Section 6.5.3).

[aa] Participants will bring the rescue medication (bottles/cartons/blisters) at each study visit to assess rescue medication compliance. Site staff should check returned paracetamol against what the participant has recorded in their diary. Participants will return all unused paracetamol at the Week 18 visit. Participants who discontinue IP early will return all unused paracetamol at the ET visit (Section 6.5.3).

[bb] Participants who discontinue IP prematurely may be given standard-of-care therapy for their pain after the ET visit as deemed appropriate by the investigator (Section 7.1.2).

[cc] The screening will be implemented until there is no perceived risk from COVID-19 for participants to take part in the study; COVID-19 symptom screening, body temperature check, and SARS-CoV-2 testing may also be conducted at other time points at the discretion of the investigator.

[dd] The SARS-CoV-2 test will be implemented until there is no perceived risk from COVID-19 for participants to take part in the study; a test sample to be taken within 72 hours prior to each dosing visit (on Days 1, 14, 28, 42, 56, and 70) (Section 4.1.2).

ABPM, ambulatory blood pressure monitoring; ADA, antidrug antibody; ACPA, anti-citrullinated protein antibodies; BMI, body mass index; COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; D or d, day(s); CCI ; DSIS, Daily Sleep Interference Scale; ECG, electrocardiogram; EOT, end of treatment; ePRO, electronic patient-reported; ET, early termination; FSH, follicle-stimulating hormone; CCI ; HIV, human immunodeficiency virus; IP, investigational product; IRT/RTSM, Interactive Response Technology/Randomisation and Trial Supply Management; KL, Kellgren and Lawrence; MRI, magnetic resonance imaging; NGF, nerve growth factor; NRS, numeric rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PD, pharmacodynamics; PGA, Patient's Global Assessment; PK, pharmacokinetics; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RPOA, rapidly progressive osteoarthritis; SAS, Survey of Autonomic Symptoms; CCI ; CCI ; SIF, subchondral insufficiency fracture; TNSn, Total Neuropathy Score-nurse; V, visit; Wk, week; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; CCI CCI

2 INTRODUCTION

2.1 Study Rationale

MEDI7352 is a bispecific fusion protein with selective, high-affinity binding to both nerve growth factor (NGF) and tumour necrosis factor-alpha (TNFα), which are mediators of both neuropathic and inflammatory pain signalling (Ji et al 2013, Lu et al 2014, Pezet and McMahon 2006). MEDI7352 is being developed for the treatment of chronic pain. This study is designed to evaluate the safety and efficacy of MEDI7352 in participants with painful osteoarthritis (OA) of the knee. Placebo is included in the study to permit comparative assessment of the safety, tolerability, and efficacy of MEDI7352 and to evaluate the benefit/risk balance of MEDI7352. This Phase IIb dose-response study will assess the efficacy and safety of multiple doses of MEDI7352 compared to placebo administered CCI CCI in participants with painful OA of the knee, prior to advancing MEDI7352 into larger clinical studies of longer duration.

2.2 Background

Chronic pain, defined as pain lasting longer than 3 months and sometimes occurring in the absence of any obvious injury or damage, is one of the most common causes for people to seek medical intervention. One of the most common causes of chronic pain and disability is OA, which is a progressive whole joint disease involving structural alterations in the hyaline articular cartilage, subchondral bone, ligaments, capsule, synovium, and periarticular muscles. The complex pathogenesis of OA involves mechanical, inflammatory, and metabolic factors, which ultimately lead to structural destruction and failure of the synovial joint.

Osteoarthritis commonly affects the hands, feet, spine, and the large weight-bearing joints such as the knees and hips although any joint in the body can be affected. As OA progresses, the affected joints appear larger, are stiff and painful, and usually feel better with gentle use but worse with excessive or prolonged use, thus distinguishing OA from rheumatoid arthritis (RA).

Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids provide accessible relief from mild-to-moderate chronic pain. However, responder rates for commonly used NSAIDs and cyclooxygenase-2 (COX-2) inhibitors are around 50% (ie, only half of patients treated will achieve meaningful pain relief). The use of opioids is also constrained by poor responder rates and potential for dependence. Use of both NSAIDs and opioids is also limited by safety concerns, including gastrointestinal bleeds and cardiovascular events with NSAIDs and constipation and respiratory depression with opioids.

MEDI7352 is a bispecific fusion protein with a single chain variable domain fragment (scFv) that binds NGF, linked by CH2 and CH3 domains of a human immunoglobulin G1 to the tumour 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 (tropomyosin-related kinase A and 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 2 biological mediators: NGF and TNF. Both mediators are considered to play important roles in sensitisation of the nervous system and pain pathophysiology (Pezet and McMahon 2006, Hefti et al 2006, Petty et al 1994, Dimitroulas et al 2017, Leung and Cahill 2010).

MEDI7352 is being developed with the goal of reducing systemic and local NGF and TNFα concentrations related to joint inflammation to more effectively treat chronic painful conditions such as OA.

Administration of MEDI7352 in nonclinical pharmacology studies using in vivo models of inflammatory pain in rodents produced significant analgesia at doses which are predicted by pharmacokinetics (PK)/pharmacodynamics (PD) modelling to sequester < 10% of circulating NGF. It is hypothesised that this analgesia at very low levels of NGF suppression results from synergy between MEDI7352 effects on NGF and TNFα binding and/or signalling pathways (see the current Investigator's Brochure [IB] for maximum and average percentage of free NGF suppression following single intravenous [IV] doses of MEDI7352 in the Phase I study D5680C00001). Therefore, MEDI7352 represents a novel analgesic approach that may avoid unwanted effects associated with high levels of NGF suppression.

Additional information regarding nonclinical studies with MEDI7352 is provided in the current IB.

2.2.1 Clinical Experience with anti-NGF and anti-TNF Therapeutics

In humans, anti-NGF antibodies have demonstrated efficacy in clinical studies of OA and chronic lower back pain (Lane et al 2010, Katz et al 2011, Brown et al 2012, Brown et al 2013, Kivitz et al 2013, Schnitzer et al 2015, Spierings et al 2013). This clinical efficacy appears to require doses of anti-NGF antibodies that are projected to sequester > 90% of circulating NGF (Neubert et al 2013).

TNF receptor blockers have a well-established role for disease modification in the management of RA and other inflammatory joint diseases in which pain is often an important component of the phenotype (Croft et al 2013). While anti-TNF therapeutics do not carry a primary indication for the provision of analgesia, there is some evidence to suggest that a selected subgroup of OA patients with a marked inflammatory profile may benefit from this therapy (Dimitroulas et al 2017).

There are well-known class effects of the individual anti-NGF and TNFα active moieties of MEDI7352, but the potential for combined effects in humans is unknown.

Potential risks of MEDI7352 based on anti-NGF and anti-TNF mechanisms of action are briefly described in Section 2.3.1.1. More detailed information about potential risks and benefits of MEDI7352 is provided in the current IB.

2.2.2 Clinical Experience with MEDI7352

As of 01 June 2021, one clinical study of MEDI7352 has been completed:

- The Phase I study D5680C00001 was a placebo-controlled, interleaved single-ascending dose (SAD) and multiple-ascending dose (MAD) clinical study in participants with pain associated with OA of the knee. The study assessed the overall safety and tolerability of MEDI7352, as well as PK, immunogenicity (presence of antidrug antibodies [ADA]), and PD. In the SAD phase, the MEDI7352 IV doses studied were 0.3, 2, 10, 50, 250, and 1000 µg/kg; the [redacted] dose was 50 µg/kg. In the MAD phase, participants received repeated IV doses (4 total) of MEDI7352 (1, 5, 50, 150, or 450 µg/kg) administered every 2 weeks.

Two clinical studies with MEDI7352 are ongoing:

- The Phase II study D5680C00002 is a randomised, double-blind, placebo-controlled, dose-response study to evaluate the efficacy and safety of MEDI7352 in participants with painful diabetic neuropathy (PDN). Participants will receive up to 6 planned IV doses administered every 2 weeks.
- The Phase I study D5680C00004 is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and immunogenicity of MEDI7352 in healthy Japanese and Caucasian volunteers. Participants will receive up to 4 planned [redacted] injections every 2 weeks.

Phase I Study D5680C00001 (Participants with Painful Osteoarthritis of the Knee)

No clinically relevant safety or tolerability concerns were raised during the dose escalation in the SAD or MAD phases of the study.

In the SAD phase, 17 of 39 participants (43.6%) treated with MEDI7352 (across all dose levels) and 9 of 14 participants (64.3%) treated with placebo had at least one treatment-emergent adverse event (TEAE). Most TEAEs were considered by the investigator to be of 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 participants 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 participants treated with placebo, the most common TEAEs were headache (28.6%) and oropharyngeal pain (14.3%).

In the MAD phase, 44 of 53 participants (83.0%) treated with MEDI7352 (across all dose levels) and 16 of 22 participants (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 participant treated with MEDI7352), which led to the participant'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 participants 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 participants treated with MEDI7352 had TEAEs of oral herpes and urinary tract infection (5.7% each) compared with participants treated with placebo (0%). However, the overall incidence of TEAEs in the SOC of infections and infestations was similar among participants treated with MEDI7352 and those treated with placebo (39.6% and 36.4%, respectively).

The most common TEAEs among participants 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 participants 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 participant 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 participants 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 participants 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).

Phase II Study D5680C00002 (Participants with Painful Diabetic Neuropathy)

The Phase II study D5680C00002 comprises 4 successive stages, each assessing MEDI7352 (up to 6 planned IV doses per participant) versus placebo as follows: Stage 1 assessed MEDI7352 5 µg/kg or placebo, Stage 2 assessed MEDI7352 150 µg/kg or placebo, Stage 3 will assess MEDI7352 450 µg/kg or placebo, and Stage 4 will assess MEDI7352 50, 150, and

450 µg/kg or placebo. At the time of preparation of this clinical study protocol (CSP), Stages 1 and 2 of the study are complete, and Stage 3 is ongoing.

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

Three participants 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, 5 µg/kg MEDI7352 or placebo)
- A TEAE of infection (symptoms of sore throat, fever, nasopharyngitis, tongue burning, and sweating) of mild intensity (Stage 2, 150 µg/kg 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 participant's withdrawal after 3 of 6 planned infusions of IP (150 µg/kg MEDI7352 or placebo).

Headache was the most commonly reported TEAE overall: 7 of 41 participants (17.1%), including 3 of 10 participants (30.0%) in the completed Stage 1 (5 µg/kg MEDI7352 or placebo), 3 of 26 participants (11.5%) in the completed Stage 2 (150 µg/kg MEDI7352 or placebo) and 1 of 5 participants (20%) in the ongoing Stage 3 (MEDI7352 450 µg/kg 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 TNSn or for parameters measured during motor and sensory nerve conduction studies.

Phase I Study D5680C00004 (Healthy Japanese and Caucasian Volunteers)

Two of the of 5 treated participants (40.0%) have had a total of 4 TEAEs as follows (one participant each): dyspepsia, catheter site erythema, injection site pain, and paraesthesia. All reported AEs were considered by the investigator to be of mild intensity. There have been no deaths, treatment-emergent SAEs, or withdrawals due to AEs.

A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI7352 is provided in the current IB.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

MEDI7352 is a novel, bispecific fusion protein targeting both soluble NGF and TNFα and, as such, the dual effect represents a novel mechanism of action. There are well-known class

effects of the individual anti-NGF and anti-TNFα active moieties of MEDI7352, as described below, but the potential for combined effects in humans is unknown. Potential risks associated with MEDI7352 administration are briefly summarised below. More detailed information about potential risks and benefits of MEDI7352 is provided in the current IB.

2.3.1.1 Potential Risks Based on Mechanisms of Action

The safety profile of MEDI7352 may include adverse reactions that are related to the expected pharmacological mechanisms of action, and thus may be comparable to those previously reported for both anti-NGF monoclonal antibodies undergoing development (eg, tanezumab, fulranumab, and fasinumab) and established anti-TNFα therapies (eg, etanercept, adalimumab, and infliximab). In addition, as with all biologics, there may be risks of immunological reactions including hypersensitivity reactions, injection site reactions, and the consequences of immunogenicity (Ingrasciotta et al 2018).

Risks Associated with the Anti-NGF Mechanism

Rapidly Progressive Osteoarthritis and other Joint Safety Events

The most common joint AE associated with anti-NGF monoclonal antibodies relates to clinical cases of RPOA (type 1 and type 2), which have been observed in large-scale clinical studies. Review of the tanezumab, fulranumab, and fasinumab programmes showed that the incidence of RPOA increased with increasing doses of anti-NGFs, particularly when these drugs were dosed concurrently with NSAIDs (FDA 2012). 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 (SIF), and pathological fracture (FDA 2021a). There was a significantly higher incidence of events in participants treated with tanezumab (3.2% and 6.2% of participants treated with tanezumab 2.5 mg and 5 mg, respectively) compared to NSAIDs (1.5% of participants) or placebo (0% of participants) (FDA 2021c). In addition, a greater proportion of participants treated with tanezumab (5.5% and 7.8% of participants treated with tanezumab 2.5 mg and 5 mg, respectively) required total joint replacements when compared to those treated with NSAIDs (2.6% of participants) or placebo (4.5% of participants) (FDA 2021a, FDA 2021c). Overall, approximately 85% of the total joint replacements occurred in joints KL grade ≥ 3 at baseline (FDA 2021c); however, some joint safety events including total joint replacement occurred in joints KL grade 0 or 1 at baseline (FDA 2021a, FDA 2021c).

It was also notable in the tanezumab programme that composite joint safety events are not limited to arthritis joints. For participants 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%) (FDA 2021b).

Sensory Abnormalities and Peripheral Neuropathy

Adverse events related to sensory abnormalities have been reported by participants in clinical studies with tanezumab (Bélanger et al 2018, Brown et al 2012, Brown et al 2013, Brown et al 2014, Ekman et al 2014, FDA 2021a, Gimbel et al 2014, Lane et al 2010, Katz et al 2011, Kivitz et al 2013, Nagashima et al 2011, Schnitzer and Marks 2015, Spierings et al 2013, Tive et al 2019). The most common of these AEs have been paraesthesia, hypoaesthesia (numbness), and burning sensation.

In a recent pooled analysis of safety data across 9 Phase III studies of tanezumab in participants with moderate-to-severe OA of the knee (Tive et al 2019), AEs of abnormal peripheral sensation were reported in tanezumab-treated participants more frequently than in participants receiving placebo or active comparator. For the majority of participants receiving tanezumab (monotherapy or in combination with NSAIDs) and whose final neurological consultations indicated a new or worsening neuropathy, the diagnosis was of some form of mononeuropathy, predominantly carpal tunnel syndrome or radiculopathy. Few participants were diagnosed with polyneuropathy (Tive et al 2019).

Additional information about this potential risk is provided in the current IB.

Autonomic Neuropathy and Sympathetic Dysfunction

According to the FDA Briefing Document for the 2021 Advisory Committee meeting for tanezumab (FDA 2021a), in the Phase III placebo-controlled studies with tanezumab, AEs of postganglionic sympathetic dysfunction (AEs of decreased sympathetic function such as bradycardia, orthostatic hypotension, hypohidrosis, syncope), occurred at observation-time adjusted rates of 20.3%, 29.1%, and 46.2% for subjects receiving placebo, tanezumab 2.5 mg, and tanezumab 5.0 mg, respectively; the imbalance was primarily driven by higher rates of bradycardia and orthostatic hypotension in the tanezumab treatment groups. In a Phase III active-controlled study, AEs of postganglionic sympathetic dysfunction occurred at observation-time adjusted rates of 37.0%, 25.7%, and 36.1% for subjects receiving NSAIDs, tanezumab 2.5 mg, and tanezumab 5.0 mg, respectively. Overall, the FDA concluded that tanezumab was not found to be associated with an increased risk of sympathetic disfunction.

Additional information about this potential risk is provided in the current IB.

Risks Associated with the Anti-TNF Mechanism

Anti-TNFα therapies have been associated with an increased risk of infection in the clinic. Infections, including serious infections such as tuberculosis (TB), bacterial sepsis, and invasive fungal infections, have been observed in participants treated with anti-TNFα therapies.

Patients older than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants may be at greater risk of infection. The risks and benefits of

treatment should be considered prior to initiating therapy in patients with underlying conditions that may predispose to infection, such as advanced or poorly controlled diabetes. Additional warnings and precautions for etanercept 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.

Additional information about this potential risk is provided in the IB.

2.3.1.2 Potential Risks Based on Class Effects

General Risks Associated with Protein Therapeutics

General risks of biologic therapies include infusion 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 acute anaphylaxis, usually occurring within 2 hours of the infusion (FDA 2014); hypersensitivity reactions; and development of ADAs. Antidrug antibodies to MEDI7352 could result in immune-complex disease (with manifestations including arthralgia, serum-sickness, and vasculitis), autoimmunity, or altered MEDI7352 levels or activity.

2.3.1.3 Considerations for Route of Administration

It is not known whether the clinical safety profile for MEDI7352 will differ according to route of administration: IV or CCI Local injection site reactions and immunogenicity may occur. The incidence of immunogenicity following CCI injection of MEDI7352 may also be affected as a function of local immune surveillance systems present in the skin.

2.3.1.4 General Risk-Mitigation Plan

At this stage of development, the risk mitigation plan for MEDI7352 includes:

- Implementation of appropriate inclusion/exclusion criteria, baseline evaluations, and restrictions applied during the conduct of the clinical studies, specifically:
  - Exclusion of concomitant oral and topical NSAID/COX-2 inhibitors use
  - Exclusion of study participants with a history of RPOA, osteonecrosis, SIF, avascular necrosis, and other significant arthropathies
  - Exclusion of study participants with pre-existing clinically significant motor neuropathy
  - Exclusion of participants with other medically significant or poorly controlled comorbidities, including significant cardiovascular disease (including Class 3 and Class 4 (NYHA 1994) heart failure)

- # Exclusion of participants with active infection and clinically important infection, including chronic, persistent, or recurrent infections or recent acute infections within 3 months prior to screening or between screening and randomisation
- # Screening for the identification and exclusion of participants with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or TB.
- # Exclusion of participants who are receiving disease-modifying antirheumatic drugs (DMARDs) and other immunosuppressants
- # Exclusion of participants with history of any underlying condition that predisposes participant to infections (such as splenectomy or primary or secondary immunodeficiency syndrome)
- # Exclusion of participants with a history of an opportunistic infection or who lived in areas with endemic fungal infections

∀ Clinical safety monitoring and assessment procedures conducted at appropriate intervals at specified clinic visits during the clinical study, specifically including:

- # Complete physical examinations at appropriate frequencies
- # Neurological examination, including peripheral nervous system examination with TNSn assessment at appropriate frequencies.
- # Follow-up (FU) required for cases of suspected occurrence or worsening of neuropathy by neurologist and on protocol-prespecified cases of bradycardia, orthostatic hypotension, syncope, anhidrosis, or hypohidrosis by a neurologist and/or cardiologist (Section 8.2.2)
- # Baseline evaluation of left ventricular ejection fraction (LVEF) using echocardiography in cases of Class 1 and Class 2 (NYHA 1994) heart failure and follow-up on cases of suspected new occurrence or worsening of heart failure by cardiologist.
- # Monitoring for AEs (including but not limited to evidence of infection, joint safety events, cancer, symptoms of neuropathy, and sympathetic autonomic dysfunction), vital signs (including orthostatic blood pressure [BP] measurements), ECGs, and safety laboratory tests (haematology, clinical chemistry including C-reactive protein (CRP), liver function tests, coagulation tests, and urinalysis) at appropriate frequencies
- # Monitoring of concomitant medication use
- # Monitoring for injection site reactions and hypersensitivity
- # Use of appropriate imaging techniques (X-ray or magnetic resonance imaging [MRI]) for evaluation of protocol-prespecified major joints at relevant time points (including baseline and FU) and at any time point (in addition to protocol-prespecified joints), when clinically indicated (Section 8.2.6).

- ∀ Independent expert adjudication of suspected or confirmed cases of possible or probable joint safety events including but not limited to RPOA, SIF, primary osteonecrosis, or pathological fracture cases that are experienced by the study participants (Section 8.2.7 and Section 9.6).
- ∀ Application of individual stopping criteria (Section 7.1.1)
- ∀ Unblinded Data and Safety Monitoring Board (DSMB) to review safety data (Section 9.6)

2.3.2 Benefit Assessment

Analgesics, ranging from paracetamol and opioids to NSAIDs and intra-articular hyaluronan, are prescribed for treating pain in OA, but their effect is often small (mean analgesic effect size from 0.15 to 0.30) and not sufficient in many patients (van der Kraan et al 2016). The use of opioids is constrained by poor responder rates and potential for dependence. NSAID and opioid use is also limited by safety concerns, including gastrointestinal bleeds and cardiovascular risks with NSAIDs and constipation, respiratory depression, and dependence with opioids.

For this reason, there is a significant medical need for drugs with improved and more sustained symptomatic effects and better tolerability for the treatment of chronic pain, including OA.

MEDI7352 has selective, high-affinity binding to both NGF and TNFα, which are mediators of both neuropathic and inflammatory pain signalling (Ji et al 2013, Lu et al 2014, Pezet and McMahon 2006). MEDI7352 is being developed with the goal of reducing systemic and local NGF and TNFα concentrations related to joint inflammation to more effectively treat chronic painful conditions such as OA.

MEDI7352 has been shown to be a highly effective analgesic in nonclinical studies, with significant efficacy observed at levels of sequestration of NGF that are significantly lower than those required for an anti-NGF antibody alone to demonstrate efficacy. Administration of MEDI7352 in a rodent chronic joint pain model produced significant analgesia at doses which, by modelling, sequester < 10% of circulating NGF. It is hypothesised that this analgesia at relatively low levels of NGF suppression results from synergistic engagement of NGF and TNF targets.

As conventional anti-NGF approaches are thought to require almost complete sequestration of NGF in both nonclinical and clinical studies, MEDI7352 represents a potential analgesic approach that may avoid unwanted effects associated with high levels of NGF suppression.

The completed first-time-in-human (FTIH) SAD/MAD study with MEDI7352 (D5680C00001) was conducted in participants with OA, rather than healthy participants, as there was the potential to observe at least some short-term efficacy signals in this population

at some of the doses being administered. [redacted]

MEDI7352 has been administered mainly to Caucasian participants to date. The ongoing study with MEDI7352 (D5680C00004) is being performed in healthy Japanese and Caucasian participants to allow a comparison of the safety, tolerability, PK and immunogenicity of MEDI7352 in both populations to support the participation of Japanese participants in ongoing and future clinical studies on MEDI7352 administered by the [redacted] route.

This Phase IIb study with MEDI7352 (D5680C00003) is being performed to characterise the dose-response relationship of MEDI7352 on pain in participants with chronic painful OA of the knee and to further assess MEDI7352 for safety, tolerability, PK, and immunogenicity (ie, ADAs) in this population.

More detailed information about the known and expected benefits and potential risks of MEDI7352 is provided in the current IB.

2.3.3 Overall Benefit/Risk Summary

MEDI7352 has the potential to address a significant unmet medical need for therapeutics with improved and sustained analgesic benefits for the symptomatic management of chronic painful conditions, including OA. The available nonclinical safety profile for MEDI7352 is supportive of administration in participants with chronic pain conditions at exposures that do not exceed those considered to be nonadverse to animals in toxicity studies performed per Good Laboratory Practice guidelines.

The clinical data available to date from single-dose and multiple-dose administration of MEDI7352 to participants with painful OA of the knee have shown that most AEs were mild or moderate in intensity and unrelated to IP. There have been no clinically significant changes or trends for changes from baseline in safety parameters, including safety laboratory tests, vital signs, ECG assessments, physical examinations, or assessments of peripheral neurology. There have been no reports of RPOA or destructive arthropathy. To date, a relatively small number of participants have been exposed to MEDI7352 across the ongoing Phase I and Phase II studies, so a full evaluation of risk/benefit is limited at present.

2.3.4 Overall Benefit/Risk Conclusion

Based on available information regarding the risks of MEDI7352 and the precautions included in the clinical studies to protect participants with OA, the risks are considered acceptable in relation to the potential long-term analgesic benefits for patients with painful OA.

Overall, no clinically important safety issues have emerged that preclude further evaluation of MEDI7352 in the relevant clinical study populations at exposures equivalent to those achieved with repeated IV doses up to 450 μg/kg. The MEDI7352 doses used in this study are supported by adequate safety margins, and the benefit-risk evaluation remains favourable for clinical development.

3 OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and associated endpoints are detailed below.

Table 2 Primary and Secondary Objectives

Objectives	Estimands descriptions/endpoints
Primary objectives	
To assess the efficacy of MEDI7352 compared to placebo on chronic pain in participants with painful OA of the knee at Week 12	• Population: Adults with moderate-to-severe chronic OA pain of the knee, persistent for 3 months or longer, not adequately controlled by standard-of-care treatments • Primary endpoint: ! Change in weekly average of daily NRS pain scores from baseline to Week 12 • Intercurrent events: ! Discontinuation due to lack of efficacy or an AE ! Discontinuation due to other reasons such as loss to follow-up or external circumstances ! Taking prohibited pain medication during the treatment period ! Taking excessive permitted rescue medication • Summary measures: ! Difference in mean changes in weekly average daily NRS pain scores between MEDI7352 doses and placebo ! An 'attributable' estimand strategy will be adopted for primary endpoint data missing or affected by any of the above intercurrent events: Missing or affected primary endpoint values will be imputed, but the method of imputation will differ depending upon the intercurrent event. Specifically, data missing due to discontinuation due to lack of efficacy or an AE will be imputed assuming an unfavourable outcome. Similarly, data affected by prohibited or excessive rescue medication will be set to missing and imputed assuming an unfavourable outcome.
Secondary objectives	
To assess the efficacy of MEDI7352 compared to placebo on additional measures of efficacy in participants with painful OA of the knee	Key secondary endpoints: • Change in the WOMAC pain subscale from baseline to Week 12 • Change in the WOMAC physical function subscale from baseline to Week 12 • Change in the PGA of OA from baseline to Week 12 Other secondary endpoints:

Table 2 Primary and Secondary Objectives

Objectives	Estimands descriptions/endpoints
	• Change in the WOMAC pain subscale from baseline to Weeks 2, 4, 6, 8, 10, and 18 • Change in the WOMAC physical function subscale from baseline to Weeks 2, 4, 6, 8, 10, and 18 • Change in the WOMAC overall scores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 18 • Change in the WOMAC stiffness scores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 18 • Change in PGA of OA from baseline to Weeks 2, 4, 8, 10, and 18 • Percentage of responders as measured by the OARSI responder index using the OMERACT-OARSI definition (Pham et al 2004) at Weeks 2, 4, 8, 12, and 18 • Percentage of participants who have achieved an improvement of ≥ 2 points in PGA of OA at Weeks 2, 4, 8, 12, and 18 • Change in the weekly average of daily NRS pain scores from baseline to Weeks 2, 4, 6, 8, 10, and 18 • Percentage of participants who have achieved ≥ 30% and ≥ 50% reductions in the weekly average of daily NRS pain scores from baseline to Weeks 2, 4, 8, 12, and 18 • Percentage of participants who have achieved ≥ 30% and ≥ 50%, reductions in WOMAC pain subscale scores at Weeks 2, 4, 8, 12, and 18. • Percentage of participants who have achieved ≥ 30% and ≥ 50% reductions in WOMAC physical function subscale at Weeks 2, 4, 8, 12, and 18
To assess the PK of MEDI7352 in participants with painful OA of the knee	• Serum concentration of MEDI7352
To assess immunogenicity of MEDI7352 in participants with painful OA of the knee	• Presence of ADA to MEDI7352 • ADA titre
Safety objectives	
To assess the safety and tolerability of MEDI7352 compared with placebo in participants with painful OA of the knee	Safety and tolerability will be evaluated based on AEs, vital signs, and clinical laboratory assessments including but not limited to: • AEs and SAEs • Physical examinations • Neurological examinations • Total Neuropathy Score-nurse • Weight • Vital signs (supine and standing BP, pulse rate, temperature, respiratory rate) • Survey of Autonomic Symptoms • 12-lead ECGs

Table 2 Primary and Secondary Objectives

Objectives	Estimands descriptions/endpoints
	• Clinical laboratory testing (haematology, chemistry, coagulation, and urinalysis) • CRP (inflammatory biomarker) • Concomitant medications and therapies • Injection site reactions • X-ray or/and MRI of large joints [a]
Exploratory objectives	
CCI [redacted]	

[a] Detailed information about the joints to be evaluated by X-ray and/or MRI is found in Section 8.2.6 and Appendix I.

[b] During the treatment period, participants can receive the ABPM device at any of the study visits between Weeks 8 and 12 (inclusive).

ABPM, ambulatory blood pressure monitoring; ADAs, antidrug antibodies; AE(s), adverse event(s); BP, blood pressure; CRP, C-reactive protein; CCI [redacted]; ECGs, electrocardiograms; CCI [redacted]; NGF, nerve growth factor; PGA, Patient's Global Assessment; MRI, magnetic resonance imaging; CCI [redacted]; NRS, numerical rating scale; OA, osteoarthritis; OMERACT-OARSI, Outcome

Measures in Rheumatology-Osteoarthritis Research Society International; PK, pharmacokinetics; RNA, ribonucleic acid; SAEs, serious adverse events; SAS, Survey of Autonomic Symptoms; CCI , CCI CCI ; WOMAC, Western Ontario and McMaster Universities Osteoarthritis; CCI CCI

4 STUDY DESIGN

4.1 Overall Design

Study D5680C00003 is a Phase IIb, multicentre, multinational, randomised, double-blind, placebo-controlled, dose-response study of MEDI7352 in participants 18 to 80 years of age (inclusive) with moderate-to-severe chronic pain of the knee during the previous 3 months or longer, caused by OA, and not adequately controlled by standard-of-care treatments. The study consists of a screening period of up to 45 days (one or more visits), a 12-week double-blind treatment period (10 scheduled visits), and a 24-week FU period (3 scheduled visits and 4 phone calls).

The participant should be randomised and IP administered within 45 days of initiating screening. One rescreening attempt is allowed (Section 5.4.1). Screening procedures may be performed at one or more visits (Table 1). Participants will start recording daily pain scores (using an 11-point numerical rating scale [NRS]), Daily Sleep Interference Scale (DSIS) scores, and rescue medication from Day -14 until the FU visit at Week 18. Participants will record WOMAC questionnaire responses at different time points throughout the study. NRS pain score recorded at the first screening visit and the daily pain scores from Day -7 to Day -1 (inclusive) will be used to determine eligibility.

All participants should undergo a diagnostic X-ray on the shoulder, knee, and hip joints during the screening period (Section 8.2.6.1). The reported features in the target knee joint should be consistent with at least Grade 2 OA on the Kellgren and Lawrence (KL) grading scale of 0 to 4 as per central reader evaluation. If other major joints (elbows, wrists, and ankles) exhibit signs or symptoms associated with OA, these should also be imaged during the screening period.

An MRI of the bilateral knees and the joints with a KL grade at baseline of ≥ 3 (per screening X-ray assessment) should be conducted during the screening period (exceptions are listed in Section 8.2.6.2). Eligibility (absence of specified joint abnormalities) will be determined by a central imaging reader. All participants must stop taking their disallowed current pain medication(s) for at least 48 hours or 5 half-lives, whichever is longer, prior to the start of the NRS pain score baseline period on Day -7 (Section 8 “Washout Period”). Participants who develop unacceptable pain at any stage of the study (including the washout period) will be permitted to initiate rescue analgesic therapy with paracetamol in a regimen that is aligned with local guidelines/label (Section 6.5.3).

After screening and confirmation of eligibility criteria, eligible participants will be randomised on Day 1 by using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM).

All patient-reported outcome measures (eg, WOMAC, Patient's Global Assessment [PGA] of OA, CCI) and blood sample collection for PK, PD, ADA, and CCI CCI (Table 1).

After baseline and predose assessments are performed, participants will receive blinded IP (MEDI7352 or placebo) at a 1:1:1:1:1 ratio. Participants will receive a total of 6 CCI injections every 2 weeks (Q2W) at the times indicated in the SoA (Table 1):

- Cohort 1: MEDI7352 CCI (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Cohort 2: MEDI7352 CCI (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Cohort 3: MEDI7352 CCI (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Cohort 4: MEDI7352 CCI (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Cohort 5: Placebo to match MEDI7352 (Day 1 and Weeks 2, 4, 6, 8 and 10)

After administration of MEDI7352 or placebo on Day 1, participants will remain at the study site for at least 4 hours after administration of IP. Safety and tolerability, including vital signs, AEs, and injection site reactions will be assessed at the time points indicated in the SoA (Table 1).

Efficacy, safety, and tolerability assessments and blood samples for PK, PD, ADA, CCI (Table 1).

During the treatment period, unscheduled X-ray assessments should be done "for cause" on any joints other than the hip joints with a KL grade at baseline of ≥ 3 (for which MRI as a first step in the assessment would be required) to follow up on any new findings or worsening of OA symptoms (including pain) considered clinically significant by the investigator. In addition, unscheduled MRIs should be done "for cause" in the knee joints or the joints with a KL grade at baseline of ≥ 3 to follow up on any newly occurring symptoms or worsening of symptoms considered clinically significant by the investigator (for exceptions, see Section 8.2.6.2). MRIs may also be performed on other joints at any point during the course of the study if clarification of X-ray findings is deemed necessary by the central reader or the RPOA Adjudication Committee (RPOA-AC), eg, to confirm or exclude diagnosis of SIF or possible osteonecrosis. The maximum treatment duration for each participant is approximately 12 weeks.

Participants who complete the treatment period will come in for their end-of-treatment (EOT) visit at Week 12 and then enter the FU period. Participants who permanently discontinue IP will be asked to complete study assessments at the early termination (ET) visit (Week 12 assessments) as soon as possible and then enter the FU period (Section 7.1.2). All participants

(ie, those who complete the treatment period and those who discontinue IP early) are expected to complete the EOT/ET visit and the 24-week FU period.

The 24-week FU period consists of 3 clinic visits (Weeks 18, 32, and 36) and 4 FU phone calls (Weeks 15, 21, 24, and 28). Safety X-ray imaging will be performed on the knee and hip joints at the Week 32 visit. The last study visit will occur at Week 36 to follow up on any new and clinically significant X-ray findings from the Week 32 visit. All FU assessments will be performed at the time points indicated in the SoA (Table 1).

This is a placebo-controlled Phase IIb study in which approximately 350 eligible participants will be randomly assigned to the IPs (one of 4 dose levels of MEDI7352 or placebo).

The study incorporates 2 interim analyses: (1) a futility analysis will take place when approximately 25% of participants are evaluable for the primary endpoint; this analysis will assess the likely success of the study outcome and will enable the sponsor to make a go/no-go decision regarding continuation of the study; and (2) an interim analysis of efficacy data will take place when approximately 50% of participants are evaluable for the primary endpoint; this analysis will enable the sponsor to plan future project-related activities, but without making any changes to the current study.

The maximum study duration for each participant is approximately 50 weeks. The overall study duration is expected to be 31 months (18 months of active screening and enrolment, 11 months of treatment and FU, and 2 months for database lock). The primary database lock is targeted to occur 2 months after the last participant has completed the Week 36 FU visit.

4.1.1 Study Conduct Mitigation During Study Disruptions due to Cases of Public Health Crisis

The guidance and risk-mitigation procedures given below will be implemented during cases of civil crisis, natural disaster, or public health crisis (eg, quarantines and resulting site closures, regional travel restrictions, and other considerations due to severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]/coronavirus disease 2019 [COVID-19] or similar pandemic infection).

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, and deemed necessary by the investigator and sponsor, these changes may include the following options:

- Local and regional regulations and/or guidelines regarding consent/reconsent of study participants should be checked and followed for obtaining consent/reconsent for the mitigation procedures and appropriate means of carrying out visits and assessments.
- Appropriate means of carrying out visits or assessments may include the following:
  - Home or remote visit: Performed by a site qualified health care provider (HCP) or HCP provided by a third-party vendor.
  - Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

Additional information regarding the options above can be found in Appendix H.

4.1.2 Additional Risk-Mitigation Procedures Implemented in the Context of the SARS-CoV-2/COVID-19 Pandemic

Additional risk mitigation procedures are to be implemented into the current CSP in the context of the current SARS-CoV-2/COVID-19 pandemic.

The objective of these risk mitigation procedures is to minimise the risk posed by SARS-CoV-2 to study participants, local investigational researchers, and other staff.

The risk-mitigation actions outlined below are guided by international and national recommendations with regard to COVID-19 as well as an ongoing evaluation by AstraZeneca of the evolving COVID-19 situation (EMA 2020, FDA 2020).

These changes will remain implemented until the risk posed by COVID-19 has diminished and with all due respect to international, national, and regional public health requirements and guidance.

The following criteria should be met at baseline (prior to the first IP administration) and prior to all subsequent dosing visits:

- Study participants must be willing to comply with all applicable national or regional public health requirements and local institutional risk mitigation procedures with respect to the COVID-19 pandemic.
- Study participants must be tested once for SARS-CoV-2 at baseline (within 72 hours prior to randomisation) and prior to all dosing visits (within 72 hours prior to IP administrations). All tests must be negative before each IP dose is administered. The SARS-CoV-2 test should have sufficient sensitivity and specificity for detection of SARS-CoV-2 and should meet the accepted local or regional public health standards for screening of asymptomatic participants. Treatment options should be discussed with the participant if the COVID-19 test is positive.
- Study participants must have a body temperature < 37.8°C and show no clinical signs and symptoms consistent with COVID-19 infection. Participants with a body temperature

37.8°C or above will be required to undergo further tests, including a COVID-19 test before they can be allowed to receive the IP.

- ∀ Where applicable, additional local requirements for the definition of a SARS-CoV-2 negative test result should be satisfied. These may include but are not necessarily limited to the need for repeating the SARS-CoV-2 test.

The following additional assessments will be performed prior to each dosing visit and as needed (per investigator's discretion):

- ∀ COVID-19 symptom screening (presence of symptoms in the last 14 days; screening conducted by the investigational site staff or by a questionnaire administered either in person or remotely, eg, by phone). Relevant symptoms include, but are not necessarily limited to, fever, cough, dyspnoea, sore throat, and loss of taste/smell.
- ∀ Body temperature will be checked prior to every dosing visit.
- ∀ Within 72 hours prior to each dosing visit, COVID-19 nose swab and/or throat/saliva swab will be performed according to local laboratory standards and protocols for sample acquisition.
- ∀ Blood sample (2 to 5 mL) for COVID-19 antibody testing may be undertaken, if required according to local risk mitigation procedures for COVID-19.

Participants with clinical signs and symptoms consistent with COVID-19 infection (eg, fever, cough, dyspnoea, sore throat, loss of taste/smell) or active COVID-19 infection confirmed by the appropriate laboratory test should not be considered eligible for IP administration. Also refer to exclusion criterion 31.

If a study participant is diagnosed with SARS-CoV-2 active infection and/or COVID-19 disease, IP administration should be interrupted and treatment should be provided according to the local area guidance; local-area quarantine guidance should also be followed. To assess if the participant meets permanent IP discontinuation criteria, refer to Sections 7.1.1, 7.1.2 and 7.1.3 for criteria for temporary and permanent discontinuation of IP and procedures for discontinuation of IP.

For participants experiencing signs and symptoms indicating COVID-19 (SARS-CoV-2) infection, the investigator should attempt to determine the infectious organism and record the AE (refer to Section 8.3 for collection and FU of AEs/serious AEs [SAEs]). If a participant presents with clinical signs and symptoms consistent with COVID-19, a SARS-CoV-2 test should be performed where possible, and the test results should be recorded in the case report form as follows:

- ∀ If the test is positive, record 'COVID-19 confirmed.'
- ∀ If the test is negative and signs and symptoms, as judged by the investigator, are not suspicious of COVID-19 infection, record either the signs and symptoms or the other diagnosis, if one has been established, as applicable AE/SAE.

∀ If a test is not available and signs and symptoms, as judged by the investigator, are highly suspicious of COVID-19 infection, record 'COVID-19 suspected.'

If other concurrent diagnoses, eg, pneumonia, are present, these should be recorded as separate AEs/SAEs.

Participant safety is paramount, and the investigator should continue to reassess the risk/benefit of continued study involvement for each study participant.

For further details on study conduct during public health crisis, refer to Appendix H.

4.2 Scientific Rationale for 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 compared to placebo. Participants must be 18 to 80 years of age (inclusive) with moderate-to-severe chronic pain of the knee during the previous 3 months or longer, caused by OA, and not adequately controlled by standard-of-care treatments. Participants will receive MEDI7352 or placebo 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 benefit/risk balance of MEDI7352. The study evaluates 4 doses of MEDI7352 (CCI [redacted]) to enable a thorough characterisation of the dose-response relationship.

The 2 pain efficacy endpoints are (1) the mean change in the weekly average of the daily NRS pain scores (as measured on an 11-point NRS from 0 to 10) from baseline to Week 12, which is the primary efficacy endpoint, and (2) the mean change in the WOMAC pain subscale from baseline to the Week 12, which is a key secondary endpoint. Both the NRS daily pain scores (Alghadir et al 2018) and WOMAC (Lundgren-Nilsson Å et al 2018) are widely-used, patient-reported outcome measurement tools used to evaluate participants with OA of the knee. The weekly average of daily NRS pain scores and the WOMAC index subscales (pain, stiffness, and physical functioning) will be used for primary and secondary efficacy evaluation of MEDI7352 versus placebo. In addition, the study design includes additional patient-reported outcome measures (eg, PGA of OA, CCI [redacted] CCI [redacted]) to support the primary outcome measure.

The study includes standard assessments to evaluate safety and tolerability, including vital signs, physical examinations, 12-lead ECGs, clinical laboratory tests, and AE collection. These safety assessments are appropriate for all study cohorts.

Pharmacokinetic sampling is included to evaluate participant exposure to multiple doses of MEDI7352 administered CCI [redacted] Pharmacodynamic assessments, including determination of plasma or serum levels of NGF CCI [redacted] are included to further

characterise the relationship between relevant OA and inflammation-related biomarkers and analgesic effects of MEDI7352 in support of the clinical programme.

4.3 Justification for Dose

In the FTIH study with MEDI7352 (D5680C00001), participants with OA have received one of the following: a single IV dose of MEDI7352 (0.3 to 1000 µg/kg), a single CC dose of MEDI7352 (50 µg/kg) or repeated IV doses of MEDI7352 (1 to 450 µg/kg). Further details of this study are provided in the IB. A brief description of the current clinical experience with MEDI7352 is provided in Section 2.2.2.

In contrast to earlier clinical studies with weight-adjusted IV dosing, this Phase IIb study will evaluate fixed doses of MEDI7352 administered by the CC route. The planned dosages in this protocol are CCI administered CC Q2W with a total of 6 planned doses per participant. The proposed CC dose range is based on the IV dose range evaluated in the SAD and MAD phases of study D5680C00001. The conversion from weight-based dosing to fixed dosing takes into account the average weight of OA participants plus one standard deviation (SD). Review of the weight distribution of OA participants in several large cohorts (Yau et al 2017) showed that the mean weight range was 79.0 to 89.5 kg, and the SD range was 16.1 to 19.0 kg. Therefore, 100 kg was used in the weight conversion to ensure that CC dosing will provide exposure similar to that observed previously in OA participants administered IV doses of MEDI7352 (study D5680C00001). In addition, upon multiple dosing, body weight is not a clinically significant covariate for exposure ($p = 0.61$), which further justifies the fixed dosing approach in future studies.

The bioavailability of MEDI7352 administered by the CC route was estimated to be 21% from comparison of single doses of 50 µg/kg CC versus single doses of 50 µg/kg IV. Given the weight and bioavailability assumptions described above, the CC doses equivalent to IV doses of 15, 50, 150, and 300 µg/kg are CCI, respectively. This CC dose range is expected to provide dose-dependent exposure and target engagement. The highest CC dose of CCI is predicted to provide an exposure that is lower than the highest (450 µg/kg) IV dose studied in the MAD phase of study D5680C00001.

The rat 26-week toxicity study provides safety margins of 3.2-fold (maximum observed concentration [C_{max}]-based) and 9.6-fold (average observed concentration over the dosing interval [$C_{average}$]-based) for a MEDI7352 CC dose of CCI, whereas the cynomolgus monkey 26-week toxicity study provides safety margins of 17-fold (C_{max}-based) and 53-fold ($C_{average}$-based). Thus, the safety margins for a repeated CC dose of CCI are considered adequate and appropriate.

4.4 End-of-Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last FU visit.

The end of the study is defined as the date of last participant's last visit in the study.

5 STUDY POPULATION

Investigators should keep a record of participants who entered screening. Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study. Participants who do not meet all the eligibility criteria will not be enrolled.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

General/Informed Consent

1 Participants must understand the nature of the study and must give signed and dated written informed consent prior to the initiation of any study procedures as described in Appendix B, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 For participants participating in the optional genetic research, a separate signed and dated optional genetic research ICF must be provided prior to collection of samples for optional genetic research that supports the Genomics Initiative. If a participant declines to participate in the genetic research, this will have no influence on the ability of a participant to participate in the study.

3 The participant should be willing and able to understand and comply with all protocol-specified restrictions and procedures and be able to use an electronic patient-reported outcome (ePRO) device as judged by the investigator.

4 The participant 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.

5 The participant must be willing and able to discontinue analgesic therapy for OA with NSAID or COX-2 inhibitors from the start of the washout period until the end of the FU period. This includes over-the-counter (OTC) pain medications and topical analgesics that contain an NSAID or COX-2 inhibitor. There are additional restrictions for medications use during the different periods of the clinical study; refer to Section 6.5 for permitted and prohibited medications.

Age/Gender/Weight

6 Study participants will be males or postmenopausal or surgically sterile females, 18 to 80 years of age (inclusive) on the day of randomisation.

Surgically sterile women are defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation. Women who are surgically sterile must provide documentation of the procedure by an operative report or by ultrasound.

Postmenopausal women are defined as follows:

- Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels are in the postmenopausal range.
- Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Note that women who are not surgically sterile must not have a positive serum pregnancy test at screening.

Men who are biologically capable of having children must agree and commit to use an adequate form of contraception (Appendix J) for the duration of the treatment period and for 3 months and 20 days after the last IP administration. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. A male participant is considered capable of having children even if his sexual partner is sterile or using contraceptives.

If the female partner of a male participant biologically capable of having children is a woman of child-bearing potential, the female partner should adhere to highly effective birth control methods (Appendix J) for the duration of the treatment period and 3 months and 20 days after the last IP administration.

7 Body mass index should be ≤ 39 kg/m^2.

Diagnostic

8 One knee must be designated as the target joint. Pain in the target joint must exceed pain experienced in other joints and must also exceed pain experienced from any concurrent medical conditions.

9 Participant should be diagnosed with OA of the target knee based on American College of Rheumatology-endorsed clinical and radiographic criteria for classification of idiopathic OA of the knee (Altman et al 1986) used in conjunction with imaging criteria in inclusion criterion 11.

10 Participant has target joint pain (OA of the knee) in the moderate-to-severe range as per investigator's judgement based on medical history data and has experienced pain most days in the 3 months prior to screening.

11 Radiological features are consistent with a diagnosis of OA in the target knee. X-ray KL grade must be ≥ 2 at target knee as evaluated by the central reader.

12 Documented history of inadequate pain relief from past or ongoing treatment according to the recommended dosing guidelines with acetaminophen (paracetamol) **and** oral NSAIDs/COX-2 inhibitors unless contraindicated/not tolerated, **and** opioids unless (a) opioids are contraindicated/not tolerated, (b) there is no access to opioids as per local standards of care, or (c) the patient is unwilling to take opioids. (Note that ongoing strong opioids are exclusionary.)

13 Participants must have a self-reported pain intensity score in the target joint ≥ 5, as assessed by an 11-point Numeric Rating Scale (NRS) during the week prior to the first screening visit.

14 A mean pain intensity score ≥ 5 in the target knee as measured on an 11-point NRS (0 to 10) by completion of a daily diary for 7 days prior to Day 1 (ie, Day -7 to Day -1, inclusive). At least 5 of 7 daily scores need to be recorded by the participant.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

General

1 Requires current treatment with another biologic therapeutic agent, DMARD, or other immunosuppressants

2 Previously received any form of anti-NGF; received anti-TNFs including but not limited to golimumab, certolizumab, infliximab, adalimumab, etanercept, or rituximab within 12 months prior to screening, or other biological DMARDs (including but not limited to abatacept, tocilizumab, and tofacitinib), or other immunosuppressants within 6 months prior to screening (with the exception of inhaled or topical corticosteroids; for exclusionary intra-articular corticosteroids use, refer to exclusion criterion 36).

3 Currently receiving strong opioids for any indication

4 Administration of COVID-19 vaccine (regardless of modality or vaccine delivery platform, eg, vector, lipid nanoparticle) within 30 days prior to randomisation (from last vaccination or booster dose, whichever is required to consider vaccination complete in line with applicable guidance)

5 Participation in another clinical study with an IP or device within 60 days or 5 half-lives, whichever is longer, prior to screening

6 Plasma donation within 28 days prior to screening or any blood donation or blood loss > 500 mL within 2 months prior to screening

7 Previous allogeneic bone marrow or stem cell transplant

8 Received nonleukocyte-depleted whole blood transfusion within 120 days prior to the genetic research sample collection, if participating in the optional genetic research

9 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

10 Diagnosis of RA. Evaluation for diagnostic purposes should include serology for anti-citrullinated protein antibodies (ACPA) at screening.

11 Participants with a documented history of gout should not be enrolled in this study. Participants with a history or diagnosis of pseudogout (calcium pyrophosphate dihydrate crystal deposition disease) can enrol if there has not been a flare within 6 months prior to screening and use of NSAIDs is not required for management of this condition.

12 Current diagnosis of a comorbid condition known to be associated with other forms of arthritis or joint pathology other than OA, including but not necessarily limited to immunological or autoimmune diseases (eg, RA, lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis); seronegative spondyloarthropathies; or other diseases involving the target joint (including endocrinopathies, metabolic joint diseases, joint infections, Paget's disease, or tumours)

Note: Non-OA causes of pain in the target knee such as anserine or patellar bursitis are exclusionary.

13 The following conditions (based on screening imaging results as per central reader evaluation) should be excluded: RPOA, primary osteonecrosis (including spontaneous osteonecrosis of the knee), SIF, avascular necrosis, osteoporotic fractures, hip dislocation, pathological fractures, or stress fracture or reaction.

14 History of significant trauma (eg, intra-articular fracture) to a knee, hip, or shoulder within 1 year prior to screening or between screening and randomisation.

15 Participants who, in the opinion of the investigator, are not suitable candidates for joint replacement surgery

16 Presence of neuropathic pain (except for pain related to tunnel neuropathies in upper limbs), or chronic primary pain syndromes (per the eleventh edition of the International Classification of Diseases): eg, fibromyalgia.

17 Presence of OA of other major joints (including but not limited to nontarget knee joint) that could interfere with assessment of pain due to OA of the target knee

18 Presence of clinically significant neuropathy (eg, hereditary, autonomic or inflammatory neuropathy).
Note: entrapment/tunnel neuropathy affecting the upper limbs that is considered stable is not necessarily excluded; sensory neuropathy that is considered stable and

non-progressive for at least 6 months is not necessarily excluded.
Note: for non-exclusionary neuropathies, there is a requirement for participants to undergo a baseline evaluation by a neurologist and to have relevant nerve conduction studies conducted and documented at baseline.

19 Requires wheelchair for mobility

20 History or current diagnosis of

Severe major depression
Psychotic disorders
Somatoform disorders
Bipolar disorders
Suicidal attempts
Hospital admission for depression within 5 years prior to screening
Or any other of psychiatric illness according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (fifth 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 participant's ability to complete the study

21 Significant cardiovascular disease including:

Class 3 or Class 4 (NYHA 1994) heart failure (ejection fraction of < 40%) or clinically significant stenosis or occlusion of a carotid or vertebral artery
Acute coronary syndrome/acute myocardial infarction, unstable angina, or coronary intervention with percutaneous coronary intervention or coronary artery bypass grafting within 6 months prior to screening
High-degree AV block II-III, clinically significant sinus node dysfunction not treated with pacemaker, heart rate of ≤ 45 beats per minute on screening ECG
Ventricular or atrial arrhythmias requiring treatment. Participants with permanent atrial fibrillation and optimally regulated ventricular rate who are not on medication with an anticoagulant are eligible.
    - NOTE: Participants designated as NYHA functional Class 1 or Class 2 are not necessarily excluded from participation. However, such participants should have LVEF measured by echocardiography and documented at baseline.

22 Significant or chronic lung disease, including severe or unstable chronic obstructive pulmonary disease, severe or unstable asthma, current pneumonitis, or interstitial lung disease

23 Diabetes complicated with retinopathy (by history) or nephropathy. Uncomplicated, stable diabetes that is well controlled and actively managed is not exclusionary. Haemoglobin A1c levels above 8.5 are exclusionary.

24 Known or suspected systemic infection, including HIV, HBV, HCV, or TB should be excluded. If QuantiFERON test is positive at screening, participants will be excluded from the study except for the cases when the QuantiFERON test remains positive after the successful treatment of TB as confirmed and documented by the relevant specialist. Other tests could be performed if deemed necessary by the investigators to exclude systemic infection. Note: Positive results of hepatitis B surface antigen (HBsAg) or antibody to hepatitis B core antigen (anti-HBc) are exclusionary.

25 Participants with a history of an opportunistic infection or who lived in areas with endemic fungal infections

26 History or evidence of demyelinating disorder, including multiple sclerosis, optic neuritis, transverse myelitis, history or current diagnosis of epilepsy

27 History of anaphylactic/severe hypersensitivity reactions, history of hypersensitivity to immunisations or immunoglobulins and/or biological therapies (eg, etanercept), or ongoing hypersensitivity reactions

28 Lifetime history of haematopoietic malignancies, history of other cancers within 5 years prior to screening except for cervical carcinoma in situ, in situ colon cancer, or non-invasive malignant colon polyps treated by excision at least 2 years ago with no evidence of recurrence. Diagnosis of any cancer between screening and randomisation.

29 Transient ischaemic attack in the last 6 months prior to screening or stroke in the last 12 months prior to screening; transient ischaemic attack or stroke between screening and randomisation

30 History of substance use disorders (SUD) including alcohol or recreational drugs according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) within 2 years prior to randomisation (with the exception of tobacco SUD)

31 Current active infection, chronic or persistent systemic infection, or serious or severe localized or systemic infection within 3 months prior to screening or between screening and randomisation, or history of any underlying condition that predisposes participant to infections (such as splenectomy or primary or secondary immunodeficiency syndrome). Note that:

Any history of severe COVID-19 infection (eg, requiring hospitalisation, intensive care unit care, or assisted ventilation) or any prior COVID-19 infection with unresolved sequelae is exclusionary. Any acute COVID-19 infection, including asymptomatic, mild, or moderate (lab confirmed or suspected based on clinical symptoms) that is not resolved 1 month prior to randomisation is exclusionary. [Note: a subject who has had an asymptomatic COVID-19 infection or recovered fully from a previous mild or moderate COVID-19 infection, without medical sequelae (including relevant negative testing that suggests they are no longer carrying

replicating SARS-COV-2 virus), and remains well for at least 1 month prior to randomisation may be considered for study eligibility].

32 Current serious or unstable clinically important illness, including respiratory, cardiovascular, gastrointestinal, endocrinologic, immunologic, haematologic, or neurological or other major disease that is likely to deteriorate or affect the participant's safety or ability to complete the study, as judged by the investigator. Note: current diagnosis of cirrhosis of the liver is exclusionary.

33 Family history of long QT syndrome

34 History of intolerability or contraindications to acetaminophen (paracetamol)

Procedural contraindications

35 History of surgery to a knee, hip, or shoulder within 1 year prior to screening or between screening and randomisation except for arthroscopy.
Note: Nondiagnostic arthroscopy performed on the target knee joint within 180 days prior to screening; or diagnostic arthroscopy performed on the target knee joint within 90 days prior to screening are exclusionary. Arthroscopy performed between screening and randomisation is exclusionary.

36 Corticosteroid injection or intra-articular hyaluronic acid injection on target knee within 12 weeks prior to screening, corticosteroid injection on a nontarget joint within 12 weeks prior to screening, or intra-articular hyaluronic acid injection on nontarget joint within 6 weeks prior to screening. If a participant has had multiple injections within the year prior to screening, then the total dose of corticosteroid used should be no more than 180 mg of triamcinolone, methylprednisolone, or their equivalent.

37 Intra-articular platelet-rich plasma treatment on the target joint within 6 months prior to screening or between screening and randomisation.

38 Received cell therapy on the target joint

39 Any medical or surgical procedure (including minor intervention) or trauma within 28 days prior to Day 1

40 Any planned surgical procedure during the duration of the study

41 Contraindications to MRI

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

42 Clinically important abnormality at screening or between screening and randomisation in physical examination, vital signs, ECG, or clinical laboratory test that may compromise the participant's safety or ability to complete the study, or the integrity of the clinical trial data, as judged by the investigator

43 Significant hypertension (defined as systolic BP of > 165 mmHg and/or diastolic BP of > 95 mmHg). If the BP results are out of range, the measurements can be repeated on the same day or at another convenient visit during screening.

44 Orthostatic hypotension (defined as a sustained reduction of systolic BP of at least 20 mmHg and/or diastolic BP of at least 10 mmHg within 3 minutes of standing from a supine position, provided that supine BP is stable). If supine BP results are not stable, the measurements can be repeated on the same day or at a subsequent screening visit. If it is not possible to establish stable supine BP, then participant is not eligible for the study.

45 Any clinically significant abnormality in ECG rhythm, conduction, or morphology as judged by the investigator.

∀ Note that a corrected QT interval by Fredericia (QTcF) interval measurement of◦>◦470◦milliseconds is exclusionary.

46 Participant with > 2 × upper limit of normal (ULN) of any of the following: ALT, aspartate aminotransferase (AST), or alkaline phosphatase (ALP) or > 1.5 × ULN total bilirubin

For participants with a test result > ULN for ALT, AST, ALP, or total bilirubin, a diagnosis or the cause of any clinically meaningful elevation must be understood and recorded in the source documents and electronic case report form (eCRF)

47 Estimated creatinine clearance ≤ 50 ml/min at screening

48 Clinically significant abnormal findings in coagulation or haematology laboratory tests

49 A positive pregnancy test at screening

50 Positive drug screen for drugs of abuse unless there is a documented medical explanation for the positive result other than drugs of abuse (eg, prescribed opioids for pain or benzodiazepines). A urine drug screen positive for cannabinoids is exclusionary unless there is a documented legitimate medical reason for the participant's cannabinoid use (eg, chronic pain) and the investigator and medical monitor agree that the participant can abstain from use for the duration of the study.

51 Participant requires aspirin at doses greater than 325 mg/day for cardiovascular prophylaxis or requires treatment with vitamin K-dependent anticoagulant (eg, warfarin).

5.3 Lifestyle and Activity Considerations

Participants should maintain their daily normal routine including stable doses of permitted medication. Participants are also permitted to continue their nonpharmacologic activities interventions during the clinical study. Participants participating in a regular prescribed physiotherapy programme should maintain this for the duration of their participation in the study. Participants should be cautioned against performing strenuous exercise regimens during the study as it may influence laboratory results and pain data. Participants may participate in light exercise and recreational activities during the study.

Participants participating in a regular homeopathy or naturopathy programme should maintain this for the duration of their participation in the study.

Refer to Section 6.5 for guidance on permitted and prohibited medications.

5.3.1 Meals and Dietary Restrictions

Participants will be asked to avoid foods containing poppy seeds for 5 days prior to the screening visit.

Participants will be asked to avoid any changes in OTC products and herbals, vitamins, and minerals from at least 14 days prior to the first IP administration on Day 1 through to the end of the FU period. 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 participant should remain in the study or be dismissed from the study. Procedures for early discontinuation of IP are provided in Section 7.1.2.

5.3.2 Tobacco Restrictions

Participants who use nicotine patches may continue to use them at the same dose and at the same time of day and must keep their smoking habit unchanged until at least Week 18 of the study. Although no change in smoking habits is preferred, smokers are permitted to quit smoking during the study. The investigator should be consulted, and the conversation documented in the participant's chart.

5.3.3 Other Restrictions

Participants must refrain from blood and plasma donation during the study and for at least 2 months after the final FU visit.

Fertile male participants must use appropriate contraception and must refrain from sperm donation from first dosing on Day 1 until at least 3 months and 20 days after the last dose of IP (Section 8.3.10).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study because they do not meet the eligibility criteria for participation in this trial (screen failure) due to, but not limited to, the following criteria: a laboratory result, test result, consent withdrawal, pain severity, disallowed medication, or other reversible condition. 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the investigator. Rescreening procedures are described below.

5.4.1 Rescreening

One rescreening attempt is permitted for each participant.

For the participants who have undergone X-ray assessments during the screening period (and provided that there were no triggering events [eg, trauma] affecting the joints or any clinically significant changes in joint condition since the X-ray evaluation during the screening period based on the investigator's assessment), then rescreening, if deemed necessary, must occur within 90 days from this first screening X-ray assessment. If it is not possible to assess such changes in clinical condition over the above-mentioned period, then the participants should not be rescreened. Note: There is no rescreening option beyond the above-mentioned 90 days for participants who have been exposed to X-rays during screening.

For the study participants who were considered screen failures before any X-ray images were obtained, one rescreening attempt is allowed at any time point while the study is ongoing.

All screening procedures and assessments (except for X-ray/MRI if performed at screening) should be repeated for the rescreened participants. A participant should sign a new ICF if they are to rescreened for any reason.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol. Study intervention (or IP) in this study refers to MEDI7352 and placebo.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The IPs that will be used in this study are outlined in Table 3.

Table 3 Investigational Products in Study D5680C00003

Intervention name	**MEDI7352**	**Placebo**
Type	**Biologic**	**Placebo**
Dose formulation	CCI	0.9% (w/v) saline
Unit dose strength(s)	CCI	N/A
Dosage level(s)	CCI Q2W	Placebo Q2W
Route of administration	CCI	
Use	Experimental	Placebo
IP and NIP	IP	IP
Sourcing	Provided centrally by the sponsor	Provided by the study site
Packaging and labelling	CCI	Provided by the study site

IP, investigational product; N/A, not applicable; NIP, non-investigational product; Q2W, every 2 weeks; CCI

CCI

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

Only participants enrolled in the study may receive IP and only authorised site staff may supply or administer IP. All IP(s) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IPs are provided in the IP manual.

6.2.1 Preparation and Administration of CCI Injections

Once randomised, participants will be dosed with either MEDI7352 (CCI) or placebo on Weeks 0 (Day 1), 2, 4, 6, 8, and 10. MEDI7352 or placebo will be administered by CCI injection.

The dose of IP for administration must be prepared by the unblinded site personnel using aseptic technique according to the detailed guidance in the IP manual. Total in-use storage time from needle puncture of the first IP vials to start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours. If storage time exceeds these limits, a new dose must be prepared from new vials.

CCI

CCI

Table 4 CCI

CCI

Using polypropylene syringes, two 1.5-mL volumes (3 mL total) should be drawn up from the vial using 18- to 19-gauge needles, and the dose delivered using 27-gauge needles. The administration time for each injection should not exceed 30 seconds. MEDI7352 does not contain preservatives and any unused portion must be discarded. Refer to the IP manual for detailed instructions for dose preparation.

Placebo is comprised of 0.9% (w/v) saline solution. To maintain the double-blind requirements, the placebo volume administered must be equivalent to the MEDI7352 volume administered for each dosing. MEDI7352 and placebo will be undistinguishable from each other when they are administered in polypropylene syringes. Unblinded site staff will prepare IP, but it must be transported and provided in a blinded manner to the person administering the IP to the participant.

Investigational product should be administrated via CC injection by an appropriately qualified and experienced member of the study site staff and where facilities to handle allergic drug reactions are available. CCI injections are to be administrated in the abdomen, anterior aspect of thigh, or into the outer area of the upper arm. Selection of the site for each injection will be at the discretion of the investigator taking into account participant preferences where possible. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard. At the same visit, both injections should be given with no more than 2 minutes between administrations.

For reporting of AEs related to injection site reactions, refer to Section 8.2.9.

6.2.2 Handling, Labelling, and Storage

AstraZeneca will provide the investigators with adequate quantities of MEDI7352 using designated distribution centres. Unblinded site personnel will prepare the IP for each participant according to the IP manual provided by AstraZeneca and the randomisation scheme.

The IP(s) 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(s) according to the dosage scheme and for ensuring proper storage of the IP(s).

The investigator (or designee) must confirm the receipt of the IP(s) with his or her signature. Until the IP is administered to the participant, it must be stored in a refrigerator at 2 to 8°C (36 to 46°F) in a secure area with restricted access.

If the IP(s) have not been refrigerated or stored properly, the excursion should be reported upon discovery. The IP(s) must be quarantined until the sponsor provides specific instructions to the site and documentation of permission to use, return, or destroy the IP(s). Use of the IP(s) prior to the sponsor's approval will be considered a protocol deviation.

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.

The IP for each participant will be prepared according to the handling instructions provided by AstraZeneca and the randomisation scheme.

6.2.3 Accountability

It is the investigator's responsibility to establish a system for handling study treatments, including IP(s). The investigator (or designee) must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP(s), including the date, quantity, batch or code number, and identification of participants (participant number) who received the IP(s). The investigator will not supply the IP(s) to any person except those named as subinvestigators and designated study personnel in this study. The investigator will not dispense the IP(s) from any study sites other than those authorised. Investigational product(s) may not be relabelled or reassigned for use by other participants. If any of the IP(s) 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 IP(s) (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(s) according to approved procedures or to return the IP(s) to the sponsor or designee for destruction.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised IP using an IRT/RTSM system. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

The IRT/RTSM will provide the investigator(s) or appropriate study personnel with the kit identification number to be allocated to the participant at the IP dosing visit.

Details for this will be described in the IRT/RTSM user manual that will be provided to each centre.

All participants, investigators, and study personnel involved in the conduct of the study will be blinded to treatment assignment. The unblinded study personnel (eg, site pharmacist) will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel. Unblinded AstraZeneca personnel who are not otherwise involved in the study will prepare data for review and interim analyses.

The IP will be administered at the study visits according to the SoA (Table 1).

6.3.1 Methods for Unblinding

Study personnel will make every effort to safeguard the integrity of the study blind to minimise 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. The randomisation code should only be broken in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, where the knowledge of the specific blinded-study intervention will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, AstraZeneca must be notified within 24 hours of breaking the blind. The investigator must document and report the

action to AstraZeneca, without revealing to the AstraZeneca staff which treatment was given to the participant.

Unblinding should be discussed in advance with the medical monitor if possible and if a participant's treatment assignment is unblinded, the investigator should contact the medical monitor for advice. If the investigator is not able to discuss treatment unblinding in advance, the investigator will document and report the action to AstraZeneca (without revealing the treatment given to the participant) to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.4 Study Intervention Compliance

Participants are dosed at the site; they will receive IP directly from the investigator or designee, under medical supervision. The date, and time if applicable, of IP dose administered in the clinic will be recorded in the source documents and in the eCRF. The dose of IP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IP. Any deviations from the planned dosing procedure will be recorded in the eCRF.

6.5 Concomitant Therapy

Any medicinal product, whether prescribed or available OTC (including herbal supplements or vitamins), is considered a concomitant medication. Any concomitant medication that the participant is receiving at the time of enrolment or during the study must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The study physician should be contacted if there are any questions regarding concomitant or prior therapy. Prior and concomitant medication use must be recorded for 28 days prior to screening through to the last FU visit as indicated in the SoA (Table 1).

Concomitant medication use may be warranted for the treatment of AEs. The use of concomitant medications to treat AEs should be discussed between the investigator and the medical monitor.

Any therapy appropriate to the participant's condition is permitted, with the exception of those listed as prohibited. Permitted concomitant medications should be maintained on a stable dose regimen during the study whenever possible.

6.5.1 Permitted Concomitant Therapy

The following treatments are permitted, with restrictions:

- Paracetamol as rescue analgesic is permitted for participants who develop unacceptable pain during the study including the washout period and the period between completion of washout and randomisation (as described in Section 6.5.3).
- Medications for the treatment of non-excluded medical conditions (eg, depression, hypertension, and diabetes mellitus) are permitted, including antihypertensive, cholesterol-lowering, and antidiabetic medications; antidepressants; and sedative/hypnotics as judged clinically acceptable by the investigator.
- Low-dose aspirin up to 325 mg/day is permitted for cerebrovascular or cardiovascular prophylaxis.
- Short-term sedation and/or analgesia if needed to perform study procedure (eg, MRI) (should not be given within 48 hours prior to a study visit or during the collection of ePRO pain data from Day -7 to Day -1 [inclusive] for baseline NRS pain evaluation).
- Limited (no more than 10 days per 8-week period) concomitant use of prescription or OTC NSAIDs may be allowed on an occasional basis for self-limiting conditions not related to osteoarthritis (eg, migraine attack), after the Week 18 FU visit. The study medical monitor should be contacted for approval prior to use whenever possible, and all doses and days of use will be recorded in the eCRF.
- Other medication considered necessary for the participant's safety and well-being may be given at the discretion of the investigator. In such cases, the reason for the introduction of the new medication should be captured in the eCRF, and an AE is expected to be reported.

If a new medication has to be introduced or the dose of concomitant medication needs to be changed during the double-blind treatment period, consultation with the medical monitor is advisable.

If the participant is receiving permitted medications for the treatment of non-excluded medical conditions, the dose must be stable for at least 28 days prior to randomisation (28 days prior to screening for serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants) and should be expected to remain stable until at least the FU visit at Week 18 of the study.

For participants who complete the treatment period, standard-of-care therapy may be given for their pain after the FU visit at Week 18 as deemed appropriate by the investigator and in alignment with local guidelines/label. However, intra-articular injections/interventions, NSAIDs, COX-2 inhibitors, and aspirin (in doses that exceed 325 mg/day) are prohibited until after the last FU visit (Visit 14).

Participants who discontinue IP early may be given standard-of-care therapy for their pain after the ET visit as deemed appropriate by the investigator and in alignment with local guidelines/label. Additional information on the allowed and prohibited medications and other procedures for early discontinuation of IP is provided in Section 7.1.2.

6.5.2 Prohibited Concomitant Medications

The following treatments are prohibited during the study:

- The use of analgesics other than paracetamol rescue medication (including but not limited to opioids, topical applications of capsaicin and formulations containing local anaesthetic for OA pain treatment) is prohibited from the start of the washout period until the Week 18 FU visit.
- The use of NSAIDs, COX-2 inhibitors for OA treatment, or use of aspirin (> 325 mg/day) at any time from the start of the washout period until after the last FU visit (Week 36) is prohibited. This includes OTC pain medications and topical analgesics that contain an NSAID or COX-2 inhibitor. For participants who discontinue IP early, NSAIDs, COX-2 inhibitors, or aspirin use is described in Section 7.1.2.
- COVID-19 vaccines
  - If a study participant is being considered for enrolment into the study and also for COVID-19 vaccination, the participant must not be randomised until 30 days after the last dose of COVID-19 vaccine or 'booster dose' (whichever is required to consider vaccination complete in line with applicable guidance). Note that this is applicable only to COVID-19 vaccines, irrespective of their modality, which are currently approved by Health Authorities or otherwise approved under relevant regulations, eg, emergency use authorisation (FDA)/conditional marketing authorisation (European Medicines Agency)/temporary supply (Medicines and Healthcare Products Regulatory Agency).
- Live viral or attenuated bacterial vaccines are disallowed from 28 days prior to the first IP dose, during IP administration, and for 2 months after the last IP administration.
- Intra-articular injections are not permitted during the study, including the screening period, with the exception of cases of ET when this treatment option is deemed necessary by the investigator. In such cases, initiation of intra-articular corticosteroid injections should be deferred until at **least 8 weeks** after the last IP administration.
- The following therapies are prohibited during the study starting from the screening period (please also refer to exclusion criteria 2, 5, 36, 51):
  - Etanercept and medications known to interact with etanercept, specifically anakinra, abatacept, and sulfasalazine
  - Other DMARDs, including but not limited to golimumab, certolizumab, infliximab, adalimumab, rituximab, tocilizumab, and tofacitinib
  - Any other form of anti-TNF or anti-NGF therapy

- # Other immunosuppressants. The restrictions related to use of intra-articular corticosteroid injections are mentioned above.
- # Vitamin K-dependent anticoagulants (eg, warfarin)
- # Oral, IV, intramuscular, or any other parenteral steroids (Note that inhaled steroids for well-controlled chronic obstructive pulmonary disease or asthma or topical steroids for eczema are permitted).
- # Any drug of abuse including but not limited to amphetamine, barbiturate, cannabis, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene, with the following exceptions:
  - Sedative/hypnotics used as described above
  - Barbiturates as a constituent of antimigraine medication (eg, Fioricet)
  - Short-term sedation and/or analgesia if needed to perform study procedure (eg, MRI). (Note: These should not be given within 48 hours prior to a study visit or during the collection of ePRO pain data from Day -7 to Day -1 [inclusive] for baseline NRS pain evaluation.)
- # Muscle relaxants, anticonvulsants, anti-Parkinsonian medications, or neuroleptic medications, unless used for non-excluded conditions, such as restless leg syndrome, are prohibited.
- # Any other investigational drug or device, including other immunotherapeutics

Participants receiving prohibited therapies will be ineligible for study enrolment or for continuation in the study (the latter at the discretion of the investigator and the sponsor).

Other medication considered necessary for the participant's safety and well-being may be given at the discretion of the investigator.

6.5.3 Rescue Medication

Participants who develop unacceptable pain during the study until the Week 18 visit or ET visit, whichever is earlier (including during the washout period and the period between completion of washout and randomisation) will be permitted to initiate rescue analgesic therapy with paracetamol using a dosing regimen that is aligned with local standards of prescribing practice and as described in the patient information leaflet and approved by the investigator. Paracetamol will be provided by the study site in its approved packaging for use as a rescue medication.

Participants will be requested not to take any paracetamol rescue medication within 24 hours prior to a study visit. Any participant who requires rescue analgesic medication for ≥ 4 days in any 7-day period should be interviewed by the study site personnel to determine if this is due to lack of efficacy or other reasons. The investigator should then determine if IP

administration should be permanently discontinued due to lack of efficacy. Participants will be instructed to keep a daily record of rescue medication use in a patient diary and the following information needs to be captured:

- Reason for use (eg, pain from the target joint, pain from other joints, non-OA pain)
- Dates and time of administration including start and end dates
- Dosage information including dose and frequency.

Rescue medication will be recorded daily from Day -14 and will continue to be recorded by the participant in their dairy until the Week 18 visit. Participants who discontinue IP early, will stop recording rescue medication after the ET visit.

Participants will bring their rescue medication (bottles/cartons/blisters) to each study visit to assess rescue medication compliance. Site staff should check returned paracetamol against what the participant has recorded in their diary. Participants should be warned to guard against taking other OTC medications containing paracetamol to avoid overuse.

If per investigator's judgement, the amount of rescue medication taken by the participant poses a risk for them to continue safely in the study, the investigator should discontinue IP. The participant will be asked to complete the study assessments at the ET visit and then enter the FU period. Procedures for early discontinuation of IP are provided in Section 7.1.2. If the rescue medication intake had been driven by pain in the target knee, the reason for discontinuation should be reported as a lack of efficacy.

Note: If paracetamol (acetaminophen) overdose is suspected, consideration should be given to the measurement of paracetamol levels and immediate referral for specialist treatment.

6.6 Dose Modification

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

6.7 Intervention after the End of the Study

After the end of the study, each participant will be treated according to standard clinical practice and local practice, at the discretion of the investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Investigational Product

It may be necessary for a participant to permanently discontinue (definitive discontinuation) IP. Participants will discontinue IP in the following situations:

- ∀ Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. Participants must be withdrawn from the study if they withdraw consent to participate. The participant should always be asked about the reason(s) and presence of any AEs.
- ∀ AE that, in the opinion of the investigator, contraindicates further dosing
- ∀ Serious noncompliance with the CSP
- ∀ Risk to participant as judged by the investigator or AstraZeneca
- ∀ If a study participant is vaccinated with a COVID-19 vaccine during the treatment period of the study, he/she should be discontinued from IP administration. The study participant will still be required to attend scheduled safety visits and to complete the follow-up period of the study (Refer to Section 7.1.2 for "Procedures for Early Discontinuation of Investigational Product"). If a study participant is vaccinated during the follow-up period, they should continue participation in the follow-up period of the study.
- ∀ Development of any of the participant-specific criteria for discontinuation (Section 7.1.1)

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

Participants will be asked to complete study assessments at the ET visit (ie, Week 12 assessments) as soon as possible and then to enter the FU period. Refer to the SoA (Table 1) for assessments to be performed at the ET visit and FU period and to Section 7.1.2 for procedures for early discontinuation of IP.

7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product

For any individual participant, further administration of IP will be stopped if any of the following scenarios occur:

- # Reports of drug-related SAE(s) or drug-related AE(s) including but not necessarily limited to:
  - o Serious or severe drug-related injection site reactions
  - o Anaphylactic reaction, defined as an immediately life-threatening allergic reaction with bronchoconstriction, angioedema, and/or hypotension (FDA 2014); or serious hypersensitivity reactions
  - o Development of moderate-to-severe sensory abnormalities (eg, paraesthesia, dysesthesia, burning, pins and needles) that are not resolved within a 14-day period
  - o Development of peripheral neuropathy
  - o New onset of demyelinating disorder
  - o Serious systemic infection
  - o Serious non-systemic infection if deemed necessary by the investigator

Any of the following are criteria for immediate and permanent discontinuation of IP (Section 8.2.11.1):
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST ≥ 3 × ULN and coexisting total bilirubin ≥ 2 × ULN (Hy's Law [HL]). Hy's law is described in Section 8.3.8 and FU of HL cases is provided in Appendix F.
  - ALT or AST ≥ 3 × ULN and coexisting international normalised ratio (INR) > 1.5
  - ALT or AST ≥ 3 × ULN and associated with symptoms (which may be either transient or persistent) of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include eosinophilia (≥ 5%), rash, or fever without clear alternative cause.
  - Any change in ALT or AST level (eg, < 3 × ULN) if there is a possibility of development of autoimmune hepatitis as per investigator's judgement. Participant should have a consult with a hepatologist, and liver chemistry values, as well as additional tests, should be completed as soon as possible (Appendix F 7)
AEs suggestive of autonomous nervous system dysfunction, including but not limited to confirmed orthostatic hypotension (Section 8.2.3.2) or significant bradycardia (Section 8.2.4) or syncope that after evaluation by a cardiologist (and/or neurologist) are considered to be a manifestation of sympathetic autonomic dysfunction
Cases when sympathetic neuropathy is not confirmed but orthostatic hypotension remains symptomatic for more than 14 days
Participants who have a proven diagnosis of sympathetic autonomic neuropathy
Development of malignancy
Development of Class 3 or Class 4 (NYHA 1994) heart failure
Positively-adjudicated possible or probable RPOA, SIF, primary osteonecrosis (including spontaneous osteonecrosis of the knee), or pathological fracture.
Participants who plan to undergo total joint replacement (knee, hip, or shoulder) or other arthroplasty procedure during the study
Haematologic toxicity, defined as one or more of the following:*
  - Leukocyte count < 2.0×10^9/L
  - Neutrophil count < 1.0×10^9/L
  - Platelet count < 75×10^9/L
    * Note: Participants must be advised to seek immediate medical attention if they develop any symptoms suggestive of blood dyscrasia or infection (eg,

persistent fever, sore throat, bruising, bleeding, or pallor). Haematology testing should be performed as soon as possible to exclude blood dyscrasia.

Development of a lupus-like syndrome, autoimmune hepatitis, or immune-complex disease

Development of COVID-19 infection that meets moderate or severe severity AE criteria.

Treatment with anti-SARS-CoV-2 monoclonal antibodies for COVID-19 infection of any severity.

Mild or asymptomatic COVID-19 infection with symptoms that have not resolved within 28 days since the last IP administration or results of appropriate testing for COVID-19 infection (ie, antigen-based) suggesting that a participant is carrying a replicating virus and remains positive within 28 days since the last IP administration.

There are other ongoing sequelae from COVID-19 infection, or the participant requires treatment for the manifestations of COVID-19 infection for the period beyond 28 days since the previous IP administration, or less than 5 half-lives have passed since the last COVID-19 antiviral medications administration within the 28-day period since the last IP administration.

If per investigator's judgement, the amount of rescue medication taken by the participant poses a risk for the participant to continue safely in the study.

7.1.2 Procedures for Early Discontinuation of Investigational Product

A participant who discontinues IP early (ie, prior to receiving the last dose of IP) should always be asked about the reason(s) and the presence of any AEs. The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

Participants who discontinue IP early will be asked to complete study assessments at the ET visit (ie, Week 12 assessments) as soon as possible and then to enter the FU period.

Participants who discontinue IP prematurely may be given standard-of-care therapy for their pain after the ET visit as deemed appropriate by the investigator and in alignment with local guidelines/label (including paracetamol, aspirin, NSAIDs, and COX-2 inhibitors if deemed necessary). However, initiation of NSAIDs, COX-2 inhibitors, and aspirin (in doses that exceed 325 mg/day) is prohibited until after 5 half-lives following the last IP administration (ie, approximately 3 weeks). Note that it is recommended to postpone NSAIDs/COX-2 inhibitors intake until 8 weeks after the last IP administration. In addition, initiation of corticosteroid therapy (eg, intra-articular injections) should be deferred until at **least 8 weeks** after the last IP administration.

Refer to the SoA (Table 1) for assessments to be performed at the ET visit and FU period. All participants prematurely discontinued from IP are expected to complete the ET visit and the 24-week FU period, which consists of 3 FU clinic visits and 4 phone calls at the times indicated below:

- ET visit: Week 12 assessments to be performed as soon as possible after the last IP administration. The following assessments/procedures will not be performed beyond the ET visit:
  - Daily NRS pain score
  - DSIS
  - Rescue medication recording
  - WOMAC
  - PGA
  - Blood collection for PK, ADA, and PD biomarkers
- FU phone call 1: To be conducted 5 weeks after the last IP administration
- FU visit 1: Week 18 assessments to be performed 8 weeks after the last IP administration
- FU phone call 2: To be conducted 11 weeks after the last IP administration
- FU phone call 3: To be conducted 14 weeks after the after the last IP administration
- FU phone call 4: To be conducted 18 weeks after the last IP administration
- FU visit 2: Week 32 assessments to be performed 22 weeks after the last IP administration
- FU visit 3: Week 36 assessments to be performed 26 weeks after the last IP administration

7.1.3 Temporary Discontinuation of Investigational Product

Withholding IP administration temporarily may be considered in the following cases:

- Development of sensory abnormalities (eg, paraesthesia, dysesthesia, burning, pins and needles) to confirm their resolution within 14 days prior to the next IP administration
- AE suggestive of new occurrence or worsening of peripheral neuropathy
- Participants who have the following sympathetic function AEs (any seriousness or severity):
  - Meet the prespecified criteria for bradycardia (Section 8.2.4)
  - Meet the prespecified criteria for confirmed orthostatic hypotension (Section 8.2.3.2)
  - Have syncope
  - Report anhidrosis or hypohidrosis
- Cases where additional evaluation or adjudication is needed to exclude possible or probable RPOA, SIF, primary osteonecrosis (including spontaneous osteonecrosis of the knee), or pathological fracture.

- ∀ Cases of signs/symptoms suggestive of worsening or new occurrence of heart failure
- ∀ When follow-up on cases of abnormal liver function is needed before the decision on permanent IP discontinuation is made (eg, identification of potential HL (PHL) cases needed or further evaluation in order to exclude HL required, or ALT or AST ≥ 5 × ULN for less than 2 weeks)
- ∀ A positive test for SARS-CoV-2 at any time point during participation in the study.
- ∀ Symptoms or signs consistent with COVID-19 infection (eg, fever, cough, dyspnoea), confirmed by an appropriate laboratory test.

Participants who meet criteria for bradycardia, orthostatic hypotension, who have had a syncope, or report anhidrosis or hypohidrosis should be evaluated by a cardiologist or neurologist as soon as possible.

Participants with AEs suggestive of new occurrence or worsening of peripheral neuropathy as per investigator's neurological assessment should be evaluated by a neurologist as soon as possible.

Participants with clinical signs/symptoms suggestive of worsening or new occurrence of heart failure should be evaluated by a cardiologist as soon as possible. Echocardiography should be performed if clinically indicated. The participant should not be dosed with the subsequent dose of IP until (if applicable) the absence of sensory abnormalities, sympathetic dysfunction, new occurrence or worsening of peripheral neuropathy or Class 3 or Class 4 (NYHA 1994) heart failure have been confirmed, or RPOA, SIF, primary osteonecrosis, or pathological fracture have been excluded.

Please refer to the Appendix F for guidance on follow-up procedures for PHL and HL cases and Section 8.2.11.1 for management of other cases of abnormal liver function.

Administration of IP can be resumed if deemed appropriate by the investigator in participants with fully resolved asymptomatic or mild COVID-19 infection (confirmed by negative SARS-CoV-2 testing (ie, antigen-based), suggesting that the participant is no longer carrying replicating virus) provided that it is completely resolved without sequalae within 28 days since the previous IP administration and participants do not require ongoing treatment for COVID-19 infection as well as do not have ongoing adverse drug reactions associated with treatment of COVID-19 infection as assessed by the investigator. Additionally, more than 5 half-lives of COVID-19 antiviral medications should elapse before IP administration is resumed. Participants who were treated with anti-SARS-CoV-2 monoclonal antibodies are not eligible for further IP administration. For participants treated with COVID-19 antiviral medications, the investigator should contact the medical monitor and agree if and when further IP administration is appropriate.

If more than 28 days have elapsed since the last IP administration, IP should be permanently discontinued. The participants will be asked to complete the ET visit as soon as possible and then enter the FU period. Refer to the SoA (Table 1) for assessments to be performed at the ET visit and FU period and to Section 7.1.2 for procedures for early discontinuation of IP.

If less than 28 days have elapsed since the last IP administration and once the above mentioned events have been evaluated/adjudicated as not meeting individual discontinuation criteria (and the participant does not meet any other IP discontinuation criteria), IP should be administrated as soon as possible. The participant should be brought back to the study schedule as soon as feasible using the allowed visit windows (provided the interval between subsequent IP administrations is not shorter than 8 days).

7.1.4 Procedures for Handling Incorrectly Enrolled or Randomised Subjects

Participants who fail to meet the eligibility criteria should not, under any circumstances, be randomised or receive IP. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomised and must be withdrawn (screen failed) from the study. A participant may be rescreened once and then be screen failed if he/she still does not meet the eligibility criteria (Section 5.4.1).

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on IP, the investigator should inform the sponsor's study physician or designee immediately.

7.2 Subject Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified FU options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an ET visit should be conducted as described in the SoA (Table 1). Participants who have received at least one dose of IP are expected to complete study assessments at the ET visit as soon as possible and then to enter the FU period (Section 7.1.2).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

Investigators must attempt to contact participants 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 8.3.

7.3 Lost to Follow-up

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

To prevent a participant being lost to FU, it is recommended that the study sites maintain up-to-date contact details for participants, including next of kin or other emergency contacts (if allowed by national regulation).

The investigator should educate the participant on the importance of maintaining contact with the investigator/study site throughout the study.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to FU, the investigator or designee must make every effort to regain contact with the participant or next of kin/emergency contact by repeated telephone calls, emails 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.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to FU. The participant will be classified as lost to FU only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study (ie, Week 36) despite all the above listed efforts. For the primary analysis purposes, a participant will be classified as lost to FU if he/she has failed to return for the required study visits and his/her vital status remains unknown at the time of primary database lock (ie, after the Week 36 visit).
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not receive IP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to FU. AstraZeneca personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix B.

8 STUDY ASSESSMENTS AND PROCEDURES

Written informed consent must be obtained from each participant prior to initiating any screening procedure. CCI [redacted]

Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

The investigator will ensure that data are recorded in the eCRFs. The web-based data capture system will be used for data collection and query handling. In addition, the investigator will ensure the accuracy and completeness of the eCRFs, including the legibility and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IP.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Data Reporting

The primary modality for study participants to capture daily information as well as complete all the study questionnaires during the study will be an ePRO hand-held device. In the event that there is a problem with the ePRO device or its availability, a digital alternative, electronic clinical outcomes assessment (eCOA) At-Home Web Back Up will be used for collecting eCOA data directly from patients when their provisioned device is not available.

Study Periods and Visits*

The study consists of a total of at least 14 visits and 4 phone calls: one (or more) screening visit(s); 10 scheduled visits during the double-blind treatment period, 3 scheduled visits during the FU period, and 4 phone calls during the FU period.

In general, patient-reported instruments should be completed by the participant upon arrival at the study site, and vital signs (including orthostatic BP) should be collected prior to any blood draws and IP administration, where applicable.

*Additional risk mitigation procedures in the context of the current SARS-CoV-2/COVID-19 pandemic are provided in Section 4.1.2.

Screening

The participant should be randomised, and IP administered within 45 days of initiating screening. A clinic visit should be scheduled approximately 14 days prior to the first dose of IP for participants to receive ePRO training and get an ambulatory blood pressure monitoring (ABPM) device (Table 1).

Screening procedures may be performed at one or more visits (Table 1). NRS pain score at the first screening visit and the daily pain scores from Day -7 to Day -1 (inclusive) will be used to determine eligibility.

Participants must have a self-reported pain intensity score in the target joint ≥ 5 (as assessed by an 11-point NRS) during the week prior to the first screening visit. All participants should undergo a diagnostic X-ray on the shoulder, knee, and hip joints during the screening period (Section 8.2.6.1). The reported features in the target knee joint should be consistent with at least Grade 2 OA on the KL grading scale of 0 to 4 as per central reader evaluation. If other major joints (elbows, wrists, and ankles) exhibit signs or symptoms associated with OA, these should also be imaged during the screening period (refer to American College of Rheumatology for the classification and reporting of OA [Altman et al 1986]).

A bilateral MRI of the knees and other joints with a KL grade at baseline of ≥ 3 (per screening X-ray assessment) should be conducted during the screening period (exceptions are listed in Section 8.2.6.2). Eligibility (absence of specified joint abnormalities) will be determined by a central imaging reader.

The central reader must confirm that the target knee meets the required KL grade criteria and that none of the specified joint abnormalities are present before participant randomisation can occur.

All screening assessments will be completed, and the results reviewed prior to the start of the NRS pain score baseline period on Day -7. Refer to the study site manual for more information on screening procedures.

Note: Serum pregnancy tests will be performed at screening only.

Screening procedures and their timing are summarised in the SoA (Table 1).

Washout Period

All participants must stop taking their current pain medication for at least 48 hours or 5 half-lives, whichever is longer, prior to the start of the daily NRS pain score baseline period on Day -7. Half-lives of commonly used pain medications are shown in Appendix K. The list is not all-inclusive. The Physician's Desk Reference provides half-life information.

Double-blind Treatment Period

The following procedures will be performed on Day 1 prior to randomisation:

- Inclusion and exclusion criteria confirmation
- Urine pregnancy test (for women who are not surgically sterile only; the results must be negative in order to proceed with IP administration)
- Urine samples for biomarkers (fasting) should be from the second morning void of the day or after. Refer to Section 8.6.1.4 for additional information.
- Daily pain diary (NRS)
- DSIS
- TNSn
- Physical and neurological examination
- Supine BP and pulse rate (prior to any blood draw)
- Orthostatic BP (after supine BP, 1 and 3 minutes after the participants stands and prior to any blood draw)
- Body temperature (prior to any blood draw)
- Respiratory rate (prior to any blood draw)
- ECG (30 to 120 minutes prior to IP administration and prior to any blood draw)
- Urinalysis

The following procedures will be performed on Day 1 after randomisation but prior to administration of IP:

- WOMAC index
- PGA
- CCI [redacted]
- CCI [redacted]
- Survey of Autonomic Symptoms (SAS)
- CCI [redacted]
- CCI [redacted]
- Blood collection for haematology, chemistry, coagulation, PK, ADA, PD, CCI [redacted] CCI [redacted]

The following procedures will be performed on Day 1 after randomisation and administration of IP:

- ECG will be performed 4 hours ± 30 minutes after IP administration.
- Supine BP and pulse rate measurements will be performed at 5 ± 5 minutes after completion of IP administration, and 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration.
- Body temperature measurements will be performed at 5 ± 5 minutes after completion of IP administration, and 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration.
- Respiratory rate measurements will be performed at 5 ± 5 minutes after completion of IP administration, and 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration.
- Injection site reactions will be monitored at approximately 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after completion of IP administration.

On the remaining dosing days, vital signs (supine BP and pulse rate, respiratory rate, and temperature) are to be assessed prior to IP administration and repeated 5 ± 5 minutes after completion of IP administration (Section 8.2.3). Orthostatic BP (Section 8.2.3.2) will be measured at all clinic visits prior to any blood draw and prior to IP administration (where applicable). Injection site reactions (Section 8.2.9) will be monitored per standard process of AE collection (participants will be instructed to report any changes that occurred at the injection site). CCI [redacted]

On study Visit 4 (Day 14) and Visit 5 (Day 28), study participants will remain under observation for at least 2 hours after IP administration.

The full list of assessments to be performed during the treatment period and timings for these assessments are provided in the SoA (Table 1).

Early Termination/Follow-up Visit

The Week 12 visit is the EOT visit for participants who complete the treatment period. For participants who discontinue IP early, the Week 12 visit is the ET visit. Participants who discontinue IP early will be asked to complete the assessments at the ET visit (Week 12 assessments) as soon as possible after IP discontinuation. Participants who discontinue IP early will follow the procedures for early discontinuation of IP (Section 7.1.2).

The 24-week FU period consists of 3 clinic visits (at Weeks 18, 32, and 36) and 4 phone calls (at Weeks 15, 21, 24, and 28). Safety X-ray imaging will be performed on the knee and hip joints at the Week 32 visit. Any potentially clinically significant findings detected on the X-ray assessment performed at the Week 32 visit will be further assessed and adjudicated (if needed) by the final FU visit at Week 36.

The full list of procedures and timing of assessments to be performed during the FU visits are provided in the SoA (Table 1).

All participants who receive IP during the study are expected to complete the FU period.

8.1 Efficacy/Pharmacodynamics Assessments

8.1.1 Daily Pain Scores

Average daily pain scores in the target joint will be recorded using an NRS. The NRS is an 11-point Likert scale used to assess pain, where participants are asked to describe their average pain in the target knee by identifying a number from 0 = "no pain" to 10 = "most severe pain imaginable over the previous 24 hours." Participants will be instructed to assess their average daily pain at approximately the same time every morning, and to record their response in a patient diary. The daily NRS pain scores recorded at the first screening visit and from Day -7 to Day -1 (inclusive) will be used to determine eligibility. The daily NRS pain scores from Day -7 to Day -1 (inclusive) will also be used to determine the baseline NRS pain. Participants will record daily pain scores from Day -14 until the Week 18 visit; participants who discontinue IP early, however, will stop recording daily NRS pain after the ET visit (Table 1).

8.1.2 Patient Global Assessment of Osteoarthritis

The PGA of OA is a 5-point Likert scale used to assess symptoms and activity impairment due to OA of the knee. Participants are asked to identify a number from 1 = very good (asymptomatic and no limitation to normal activities) to 5 = very poor (very severe symptoms which are intolerable and inability to carry out all normal activities) based on the question "Considering all the ways that OA of the knee affects you, how are you feeling today?" Participants will record their responses at the times indicated in the SoA (Table 1). On dosing days, the PGA of OA will be completed prior to IP administration. Participants who complete the treatment period will have their last PGA of OA at the Week 18 visit; participants who discontinue IP early will have their last PGA of OA assessment at the ET visit (Table 1).

8.1.3 Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC multiscale index is used to assess pain, stiffness, and joint functionality in the past 48 hours in participants with OA of the knee or hip. Participants will record their WOMAC questionnaire responses at the times indicated in the SoA (Table 1). Participants

who complete the treatment period will have their last WOMAC at the Week 18 visit; participants who discontinue IP early will have their last WOMAC assessment at the ET visit.

The WOMAC questionnaire will be completed for the target knee. On dosing days, the WOMAC questionnaire will be completed prior to IP administration.

The WOMAC pain subscale consists of 5 questions assessing the participant's pain due to OA in the target knee. Each question is scored on an NRS scale from 0 to 10, and the WOMAC pain subscale score is calculated as the mean score from all 5 questions, where higher scores represent higher pain.

The WOMAC physical function subscale consists of 17 questions assessing the participant's difficulty in performing activities of daily living due to OA in the target knee. Each question is scored on an NRS scale from 0 to 10, and the WOMAC physical function subscale score is calculated as the mean score from all 17 questions, where higher scores represent worse function.

The WOMAC stiffness function subscale consists of 2 questions assessing stiffness due to OA in the target knee. Stiffness is defined as a sensation of decreased ease of movement in the target knee. Each question is scored on an NRS scale from 0 to 10, and the WOMAC stiffness function subscale score is calculated as the mean score from the 2 questions, where higher scores represent higher stiffness.

8.1.4 Daily Sleep Interference Scale

Participants will assess how their pain interferes with their sleep using the DSIS. The DSIS is an 11-point Likert scale, with 0 = pain did not interfere with sleep and 10 = pain completely interfered with sleep. The DSIS is completed by participants via a patient diary once a day (upon awakening) to accurately capture variability in sleep interference due to pain on a daily basis, thus minimising recall bias. Participants will record DSIS from Day -14 until the Week 18 visit as indicated in the SoA (Table 1); participants who discontinue IP early, however, will stop recording DSIS after the ET visit.

8.1.5 36-Item Short Form Health Survey Questionnaire (acute recall)

The 36-Item Short Form Health Survey Questionnaire version 2 (SF-36v2) is a 36-item, self-report survey of functional health and well-being, with a 1- to 4-week recall period (Maruish 2011). Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'health transition' item, asks participants to rate how their current state of health compared to their state of health one year ago, and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF),

role limitations due to emotional problems (RE), and mental health (MH). Psychometrically-based physical and mental health component summary scores (PCS and MCS, respectively) are computed from subscale scores to give a broader metric of physical and mental health-related quality of life.

Two types of thresholds have been developed for interpretation of SF-36v2 scores. The first type is suitable for comparing group mean scores and is generally referred to as the minimally clinically important difference. The second type is suitable for interpreting change at the individual level and is referred to as the responder threshold or responder definition (Table 5) (Maruish 2011).

Table 5 Threshold values for the SF-36v2 scale and summary measures

	SF-36v2 score									
Threshold	PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
Group difference	2	3	3	3	3	2	2	3	4	3
Individual change	3.4	4.6	4.3	3.4	6.2	7.2	6.2	6.9	4.5	6.2

BP, bodily pain; GH, general health perceptions; MCS, mental health summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, emotional problems; RP, role limitations due to physical health; SF, social functioning; VT vitality

The participant will complete the SF-36v2 on the ePRO device as specified in Table 1. Any within-window assessment that has not been completed prior to the scheduled visit will be completed at the site prior to other study procedures.

8.1.6 European Quality of Life-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L™ questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty. The questionnaire score is translated into an index value or utility score. The EQ-5D-5L is a self-administered questionnaire.

The participant will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state. Participants will record their responses at the study site at the times indicated in the SoA (Table 1).

8.1.7 WPAI:OA questionnaire

The WPAI:OA is a self-administered tool comprised of 6 questions that measure absenteeism, presenteeism, work productivity, and activity impairment due to OA of knee. This tool captures data from the past 7 days. Each subscale score is expressed as a percentage impairment from 0 to 100, where higher numbers indicate greater impairment and less productivity.

The participant will complete the WPAI:OA at the times indicated in the SoA (Table 1). Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.8 Assessment of Healthcare Resource Utilisation

The utilisation of healthcare resources (eg, doctor office visits, hospitalisations, surgeries, or other procedures) used by participants prior to entering the study (ie, 3 months prior to baseline) and during the study will be assessed at the times indicated in the SoA (Table 1).

Healthcare resource utilisation data associated with medical encounters will be collected by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. After the baseline assessment, the question should be asked by recalling the period between visits.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalisation (total days or length of stay, including duration by wards (eg, intensive care unit)
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

The following HCRU resources should be collected:

- Services:
  - Primary care physician visits
  - Neurologist visits
  - Rheumatologist visits
  - General practitioner or nurse practitioner
  - Pain specialist visits
  - Orthopaedists

- # Physical therapists
- # Chiropractors
- # Alternative medicine or therapy (concomitant medications)
- # Podiatrist
- # Nutritionist/Dietician
- # Radiologist
- # Home Healthcare services
- # Other

∀ Emergency department visits
∀ Hospitalisation for knee OA
∀ Aid/devices:

- # Wheelchair
- # Walking
- # Device or utensils to help with dressing, bathing, or eating

∀ A question on how OA has interfered with work activities can also be asked:

- # Did you quit your job because of OA?
- # How long before you quit your job because of your OA?

8.1.9 Rescue Medication

Rescue medication will be recorded daily from Day -14 and will continue to be recorded by the participant in their diary until the Week 18 visit as indicated in the SoA (Table 1). Participants who discontinue IP early, will stop recording rescue medication after the ET visit.

The dosage strength of the paracetamol tablets and the number of tables taken in a 24-hour period should be recorded by the participant.

The participant will be asked in the diary a question similar to the following: “Have you used any paracetamol in the last 24 hours?” The participants will respond: Yes or No

If yes, record the following:

∀ Reason for use (eg, pain from the target joint, pain from other joints, non-OA pain)
∀ Dates and time of administration including start and end dates
∀ Dosage information including dose and frequency.

Rescue medication use (number of days, cumulative consumption) from baseline to Weeks 4, 8, 12, and 18 (Note: Week 18 only for participants who completed the treatment period) will be compared between participants taking MEDI7352 or placebo.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

A physical examination will be performed and include assessments of the following: general appearance, skin, head and neck, examination of the oral cavity for any lesions, lymph nodes, thyroid, abdomen (bowel sounds, liver, and spleen palpation), back (including costovertebral angle tenderness), musculoskeletal/extremities, cardiovascular, and respiratory systems.

If clinical signs/symptoms suggestive of worsening or new occurrence of heart failure are noted, a consultation with a cardiologist should be obtained as soon as possible. Echocardiography should be performed if clinically indicated. Participants designated as NYHA functional Class 1 or Class 2 should have LVEF measured by echocardiography and documented at baseline.

The participant should not be dosed with the subsequent dose of IP until the absence of Class 3 or Class 4 (NYHA 1994) heart failure has been confirmed (refer to the Section 7.1.3).

Height and weight will be measured at screening and weight at the Week 12 visit. Weight should also be measured when change is suspected or fluid retention occurs.

8.2.2 Neurological Examinations

The neurological examination should be performed by a neurologist or an appropriately experienced physician and will include assessment of mental status, cranial nerves, motor examination (muscle strength and tone), upper and lower extremity deep tendon reflexes, plantar responses, sensory system examination, coordination, and gait. Also information about presence of anhidrosis or hypohidrosis should be collected during the examination.

Ideally, the neurological examination should be performed by the same examiner at each clinic visit.

A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs:

- An AE suggestive of new occurrence or worsening of peripheral neuropathy
- AE of new occurrence or worsening of abnormal sensation such as allodynia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, or sensory loss
- A new or worse clinically significant abnormality on the neurological exam (in addition to the guidance above)
- A neurological AE considered medically important by the investigator

If the participant experiences any of the events above, a neurological examination by a consulting neurologist should be obtained as soon as possible (including a nerve conduction velocity test if deemed necessary by the neurologist) after these signs and symptoms are identified.

For participants with clinical manifestations consistent with worsening of pre-existing neuropathy, follow-up nerve conduction studies should be performed and documented at the time points deemed appropriate by the neurologist, but at least once during participation in the study. The results should be recorded in the appropriate eCRF. Adverse events should be reported where applicable as described in Section 8.3 and Appendix C.

The participant should not be dosed with the subsequent dose of IP until the absence of the neurological condition that meets prespecified criteria for IP discontinuation has been confirmed. Refer to Section 7.1.1 for prespecified criteria for discontinuation of IP and Section 7.1.3 for temporary discontinuation of IP.

Cases of anhidrosis or hypohidrosis should be further evaluated by a neurologist (or another relevant specialist trained in the assessment of autonomic nervous function, eg, cardiologist) to exclude presence of sympathetic autonomic neuropathy as soon as possible.

The participant should not be dosed with the subsequent dose of IP until the absence of autonomic neuropathy has been confirmed.

If sympathetic autonomic neuropathy is not confirmed and the participant does not meet other individual IP discontinuation criteria, the participant can continue in the study as planned provided no more than 28 days passed since last IP administration (Section 7.1.3).

8.2.3 Vital Signs

8.2.3.1 Blood Pressure and Pulse Rate

At each clinic visit, BP and pulse rate should be taken using a standard sphygmomanometer after the participant has rested in a supine position for at least 5 minutes (10 minutes when supine BP and pulse rate measurements are followed by orthostatic BP evaluation).

On all dosing days, BP and pulse rate are to be assessed prior to any blood draw and IP administration and repeated 5 ± 5 minutes after completion of IP administration. Additional measurements of supine BP and pulse rate will be taken on Day 1 at the following time points: 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration.

8.2.3.2 Orthostatic Blood Pressure Measurements and Follow-up of Confirmed Orthostatic Hypotension

Orthostatic BP measurements will be obtained at all clinic visits using a standard sphygmomanometer and taken after scheduled supine measurements (1 and 3 minutes after the participant stands) and prior to any required blood draw or IP administration (and prior to randomisation on Day 1).

To minimise chances of orthostatic hypotension related to volume depletion, participants should be well hydrated when they come to the clinic for study visits. Investigators should advise that participants drink 8 to 16 ounces (240 to 480 mL) of water prior to reporting for the study visit.

Supine BP measures will be collected after participants have been lying down for at least 10 minutes. To ensure that a stable supine BP is obtained, at least 2 systolic and 2 diastolic BP measurements will be obtained. If the replicate measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine BP will be considered stable. The mean value of each replicate (mean systolic and mean diastolic value) will represent the baseline BP for that visit. After stable BP is achieved, the participant will stand and a BP measurement will be taken at 1 and 3 minutes after the participant stands. If the BP measurements do not meet the criteria for orthostatic hypotension, no additional measurement is needed (refer to exclusion criterion 43 for screening visit and Visit 2 assessments and Table 6 for the assessments after Visit 2). If BP measurements taken at the screening visit or Visit 2 meet exclusion criterion 43, then the participant is not eligible for participation in the study. After Visit 2 (Day 1), if the initial BP measurement meets any of the criteria shown in Table 6, investigators will repeat the supine and standing measurements up to 2 additional times.

Table 6 Orthostatic Blood Pressure Criteria and Management

Mean supine systolic BP	Decrease in BP indicative of orthostatic hypotension	Actions for both criteria
≤ 150 mmHg	≥ 20 mmHg systolic or ≥ 10 mmHg diastolic	Repeats the BP measurements (supine and standing) up to 2 additional times. • If either the 1 minute or 3 minute standing BP meets the orthostatic (postural) hypotension criteria, then the sequence is considered indicative of orthostatic hypotension. • If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is confirmed and an AE of orthostatic hypotension will be reported.
> 150 mmHg	≥ 30 mmHg systolic or ≥ 15 mmHg diastolic	

AE, adverse event; BP, blood pressure

Blood pressure changes meeting the prespecified criteria and confirmed as described above will be designated as a confirmed orthostatic hypotension episode. The event should be

reported as an AE whether or not the participant had accompanying symptoms. If a confirmed case of orthostatic hypotension occurs, the participant should be evaluated as soon as possible by a neurologist or cardiologist in order to determine the presence of sympathetic autonomic neuropathy. The participant should **not** receive further administration of IP until absence of sympathetic neuropathy is confirmed.

- If sympathetic neuropathy is confirmed, administration of IP will be permanently discontinued, and the participant will be asked to complete the assessments at the ET visit (Week 12 assessments) and then to enter the FU period (Section 7.1.2).
- If sympathetic neuropathy is not confirmed and orthostatic hypotension is not symptomatic, the participant can continue in the study as planned provided no more than 28 days passed since last IP administration (Section 7.1.3).
- If sympathetic neuropathy is not confirmed but orthostatic hypotension remains symptomatic for more than 14 days, administration of IP will be permanently discontinued, and the participant will be asked to complete the assessments at the ET visit (Week 12 assessments) and then to enter the FU period (Section 7.1.2).

Refer to the SoA (Table 1) for assessments to be performed at the ET visit and the FU period and Section 7.1.2 for procedures for early discontinuation of IP.

8.2.3.3 Blood Pressure Measured by an Ambulatory Blood Pressure Monitoring Device

Participants will be given training at their local study site about how to set up and apply the ABPM device. In brief, an appropriate size cuff encircling 80% to 100% of the arm will be selected and the device will be fitted to the nondominant arm of the participant, with the bladder placed over the artery, and an initial test reading performed. The participants will be advised that for the first reading the device will inflate to a pressure of 180 mm Hg, and thereafter the device will adapt to inflate to a pressure just above the last recorded BP. The participant will be advised to undergo normal daily activities while wearing the cuff, and he/she will be advised to avoid any strenuous form of activity, bathing, or showering while wearing the cuff. The participant will be advised to remain still during a measurement with the arm relaxed at heart level. The participant will also be given advice on how to wear the device during the day and at night while sleeping, and what to expect in terms of frequency of readings during the day (every 15 minutes) and overnight (every 30 minutes). During ABPM, systolic BP, diastolic BP, pulse pressure, pulse rate, and mean arterial pressure readings will be recorded over a period of 24 hours.

Participants will wear the ABPM device for a period of 24 hours at 2 separate times during the study: one time during the screening period and one time during the double-blind treatment period (between Weeks 8 and 12) (Table 1). Participants will receive the ABPM device at the study site, and training will be provided. The participant will wear the monitor/cuff for approximately 24 hours (including overnight at home) and will remove the device at home at

the end of the 24-hour period. Participants will return the device to the clinic at their next scheduled study visit after completing the 24-hour ABPM measurement.

8.2.3.4 Body Temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the visits and times indicated in the SoA (Table 1).

Body temperature will be taken at all clinic visits. On all dosing days, vital signs (including body temperature) are to be assessed prior to any blood draw and IP administration (and prior to randomisation on Day 1) and repeated 5 ± 5 minutes after completion of IP administration. On Day 1, body temperature will also be assessed at the following time points: 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration.

8.2.3.5 Respiratory Rate

Respiratory rate will be measured in breaths per minute by observation at the visits and times indicated in the SoA (Table 1).

Respiratory rate will be measured at all clinic visits. On all dosing days, vital signs (including respiratory rate) are to be assessed prior to any blood draw and IP administration (and prior to randomisation on Day 1) and repeated 5 ± 5 minutes after completion of IP administration. On Day 1, respiratory rate will also be assessed at the following time points: 30 ± 5 minutes, 60 ± 10 minutes, 2 hours ± 10 minutes, and 4 hours ± 10 minutes after the start of IP administration.

8.2.4 Electrocardiograms

At the visits and time points specified in the SoA (Table 1), a 10-second, 12-lead safety ECG will be obtained after 10 minutes of supine rest, using the study site's own ECG machines.

On Day 1, ECG recording will be performed 30 to 120 minutes prior to IP administration (and prior to randomisation) and 4 hours ± 30 minutes after IP administration. On all other dosing days, ECG recording will be performed at 30 to 120 minutes prior to IP administration; thereafter, ECGs will be recorded at Week 12 and Week 32. ECG recording should be performed prior to any blood draw.

The investigator will judge the overall interpretation as normal or abnormal clinically nonsignificant or abnormal clinically significant, and this evaluation will be reported in the eCRF. Clinically significant findings should also be documented on the AE page of the CRF if applicable. The PI may add extra 12-lead resting ECG safety assessments, if needed. These assessments should be entered as an unscheduled assessment.

Cardiovascular findings that are considered to be potential indicators of sympathetic nervous system dysfunction should be evaluated by a cardiologist or neurologist as soon as possible. Such findings include but are not necessarily limited to significant bradycardia (defined as pulse rate of ≤ 45 beats per minute on an ECG). (Note that this value is exclusionary at screening.)

8.2.5 Survey of Autonomic Symptoms (SAS)

The SAS is a validated, easily administered instrument to measure autonomic symptoms and has been proposed as a valuable tool in assessing autonomic neuropathies in clinical trials (Zilliox et al 2011).

The SAS scale evaluates the presence of symptoms and the degree of severity. The SAS consists of 11 questions in women and 12 questions in men. Each question has a Yes or No answer to symptoms occurring 6 months prior to IP administration. Questions answered with "Yes" are further rated from 1 to 5 by asking the participant how much each symptom is bothering him or her. Each answer is scored on a scale from 1 to 5 where 1 = not at all and 5 = a lot, and a total symptom impact score is determined.

The questions in the questionnaire assess the following domains: orthostatic, sudomotor symptoms, vasomotor, gastrointestinal, urinary, and sexual dysfunction.

Participants will complete the SAS at the times indicated in the SoA (Table 1).

8.2.6 Imaging

8.2.6.1 Radiographic (X-ray) Assessment

A diagnostic X-ray should be performed for all participants during the screening period on the shoulder, knee, and hip joints. The reported features in the target knee joint should be consistent with at least Grade 2 OA on the KL grading scale of 0 to 4 as per central reader evaluation.

Central radiology readers will review the X-ray images for assessment of eligibility criteria including the KL grade and exclusionary joint conditions as described in the exclusion criteria (see exclusion criteria 10, 12, 13, and 17). Participants must not start IP until the X-ray data is reviewed, and eligibility criteria are confirmed.

If other major joints (elbows, wrists, and ankles) exhibit signs or symptoms associated with OA, these should also be imaged via X-ray during the screening period (Also refer to American College of Rheumatology for the classification and reporting of OA [Altman et al 1986]).

At the Week 32 visit, safety X-ray imaging will be performed on the knee and hip joints. Any potentially clinically significant findings detected on X-ray performed at Week 32 will be

further assessed and adjudicated (if needed) by the final FU visit (Week 36). Any AEs or AEs of special interest (AESIs) related to X-ray findings reported will be followed as long as deemed medically necessary (ie, until resolution, stabilisation, the event is otherwise explained, or the participant is lost to FU).

In addition, an unscheduled X-ray should be done "for cause" for any joints except for hip joints with a KL grade at baseline of ≥ 3 (for which an MRI as a first step of the assessment is required) to follow up on any worsening of symptoms (including pain) considered clinically significant by the investigator. Note that X-ray for hip joints with KL grade at screening ≥ 3 might be performed as well if deemed necessary by the investigators or RPOA-AC.

After study Day 1, central radiologists will review radiographic images taken "for cause", eg, to follow up on any newly occurring symptoms or worsening of symptoms (including pain) considered clinically significant by the investigator or due to joint-related AEs warranting further evaluation by the RPOA-AC. The adjudication committee will review cases of suspected joint safety events (including but not limited to RPOA, SIF, primary osteonecrosis (including spontaneous osteonecrosis of the knee), or pathological fracture cases) to determine whether or not they meet accepted diagnostic criteria.

For assessment of joint safety events, see Section 8.2.7.

Certified X-ray technologists performing X-ray of the knees or other major joints will be trained in the appropriate radiographic protocols for the study. All X-ray technologists will be approved by AstraZeneca or its representative before they can perform any X-ray deemed necessary for the study.

Details of the image acquisition will be described in the Procedure Manuals for X-ray and MRI Image Acquisition.

8.2.6.2 Magnetic Resonance Imaging

MRI of the bilateral knee joints must be done during the screening period (Table 1) except for the cases when a study participant has undergone a total joint replacement and has an artificial nontarget joint or when a knee joint is no longer present due to leg amputation. In that case only acquire MRI images of the opposite (target) knee. An MRI should also be performed during the screening period for the joints with a KL grade at baseline of ≥ 3 as per screening X-ray assessment.

Eligibility (absence of specified joint abnormalities) will be determined by a central imaging reader.

In addition, unscheduled MRIs should be done "for cause" in the knee joints or the joints with a KL grade at baseline of ≥ 3 to follow up on any newly occurring symptoms or worsening of

symptoms considered clinically significant by the investigator (except for the cases when a study participant has undergone a total joint replacement and has an artificial joint).

An MRI may also be performed for imaging of any other joints at any other point during the study if clarification of X-ray findings is deemed necessary as per the central reader/RPOA-AC (eg, to confirm/exclude diagnosis of a SIF or possible osteonecrosis).

Details of the image acquisition will be described in the Procedure Manuals for X-ray and MRI Image Acquisition.

8.2.7 Follow-up of Clinically Significant Findings in Major Joints

Any participant who based on the investigator's assessment has clinically significant findings related to major joints should undergo the following assessments as soon as possible:

- ∀ X-ray should be done for any joints except for hip joints with KL grade at screening ≥ 3 (for which an MRI as a first step of the assessment is required*).
- ∀ MRI of knee joints or the joints with a KL grade at baseline of ≥ 3 (which required MRI at baseline)

*Note: X-ray for hip joints with KL grade at screening ≥ 3 might be performed as well if deemed necessary by the investigators or RPOA-AC.

X-ray images (and MRI if performed) will be sent to the central reader for review and assessment. The RPOA-AC will review cases of suspected joint safety events (including but not limited to RPOA, SIF, primary osteonecrosis (including spontaneous osteonecrosis of the knee), or pathological fracture cases) to determine whether or not they meet accepted diagnostic criteria. The RPOA-AC will also review all joint safety events that meet SAE or severe AE criteria.

Participants should not be administered with the subsequent dose of IP until RPOA, SIF, primary osteonecrosis (including spontaneous osteonecrosis of the knee), or pathological fracture cases are excluded based on central reader assessment and, if required, adjudicated by the RPOA-AC (Section 7.1.3).

Participants who prematurely discontinue IP due to positively-adjudicated possible or probable RPOA, SIF, primary osteonecrosis (including spontaneous osteonecrosis of the knee), or pathological fracture cases will be asked to complete the study assessments at the ET visit (Table 1) and then to enter the FU period. Any AEs or AESIs related to joint safety events will be followed as long as deemed medically necessary (ie, until resolution, stabilisation, the event is otherwise explained, or the participant is lost to FU). Procedures for early discontinuation of IP are provided in Section 7.1.2.

For additional information regarding the RPOA-AC refer to Section 9.6 and Appendix B 5.

8.2.8 Total Neuropathy Scores-Nurse

The TNSn, a semiquantitative clinical assessment of peripheral nervous system function, will be administered at the times indicated in the SoA (Table 1). The TNSn provides for an assessment of sensory symptoms, 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. Each domain of the TNSn is scored from 0 to 4 with a total score ranging from 0 to 20. Details on administration of the assessment and scoring will be described in the study site manual.

8.2.9 Injection Site Reactions

Investigators should evaluate injection site reactions that occur during or immediately following IP administration per the FDA Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products (FDA 2014) and FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007). See Section 2.3 for potential risks related to injection site reactions.

Investigators should evaluate injection site reactions using the toxicity grading scale summarised in Table 7.

Table 7 Local Reaction to Injectable Product

Local Reaction	Mild	Moderate	Severe [a]
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 [b]	2.5 to 5 cm	5.1 to 10 cm	> 10 cm
Induration/swelling [c]	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

[a] In addition, the reactions in which ulceration or severe necrosis occurs should be considered as severe as per CTCAE v5.

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

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

CTCAE, common terminology criteria for adverse events

Source: FDA 2007

Injection site reactions will be monitored at the study visits indicated in the SoA (Table 1). On Day 1, injection site reactions will be monitored at approximately 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after completion of IP administration. On other dosing days, injection site reactions will be monitored per standard process of AE collection (participants will be instructed to report any changes occurred at the injection site).

8.2.10 Procedures for Subjects Undergoing Joint Replacement

Participants who have undergone or plan to undergo total joint replacement or other arthroplasty procedures during the study should discontinue IP. It is recommended to have at least 3 weeks between IP administration and joint replacement surgery. Participants will be asked to complete study assessments at the ET visit as soon as possible and then to enter the FU period. Refer to the SoA (Table 1) for assessments to be performed at the ET visit and FU period and to Section 7.1.2 for procedures for early discontinuation of IP.

All available information including but not limited to prior orthopaedic consultations, imaging studies of the affected joint, preoperative assessments, and results of histopathological examination will be collected. Wherever possible, the surgeon's assessment of procedural difficulty (uneventful; minor complications (including but not limited to impaired wound healing); or major complications (taking into consideration the participant's medical history and physical condition prior to surgery) should be collected as well.

The RPOA-AC will review and adjudicate all joint safety events that led to joint replacement or other arthroplasty procedures.

AEs that led to joint replacement surgery should be followed up by the investigator for as long as medically indicated but no less than up to the end of the FU period or 4 months since joint replacement surgery (whichever is longer). Data on additional or corrective procedures (for example a revision or implant replacement) that were necessary after total joint replacement and their outcomes should be collected wherever possible as well.

AstraZeneca retains the right to request additional information for any participant who had undergone joint replacement at the end of the study if deemed necessary.

8.2.11 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, serology, drug screening, pregnancy tests, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units and reference ranges) will be recorded in the eCRF.

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

Samples for laboratory tests will include the following:

- Haematology: haemoglobin, haematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, platelet count (or estimate), white blood cell count, and white blood cell differential
- Serum chemistry: albumin, total and direct bilirubin, total protein, calcium, ALP, ALT, AST, gamma glutamyl transferase, blood urea nitrogen, creatinine*, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, lactate dehydrogenase, uric acid, CRP, cholesterol, triglycerides, creatine phosphokinase. Procedures for following up on abnormal liver function tests are described in Section 8.2.11.1.

  *Note: Serum chemistry reports should include calculation of creatinine clearance using the Cockcroft-Gault equation.

- Coagulation panel: prothrombin time, activated partial thromboplastin time, fibrinogen
- Urinalysis: pH, specific gravity, blood, leukocytes, glucose, protein, ketones, bilirubin
- Urine drug screen: including but not limited to amphetamine, barbiturate, cannabinoids, cocaine, methadone, methaqualone, opiate, phencyclidine, and propoxyphene. A general urine drug screen will be performed at screening and a urine screen for opiates only will be performed at the Week 2 visit.
- Urine pregnancy test
- Serology: HIV, hepatitis B, and hepatitis C screen, TB (QuantiFERON), and ACPA (screening only)
- Endocrinology: FSH (Female < 50 years of age only and at screening only, to confirm menopausal state), β-HCG beta human chorionic gonadotropin (female participants, not surgically sterile only, at screening only).
- Other: haemoglobin A1c

Clinical laboratory tests (haematology, chemistry, or coagulation) could be repeated at the discretion of the investigator during screening if clinically indicated.

Instructions for sample collection, processing, storage, and shipment are provided in the study site manual.

8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests

Evaluation of abnormal liver function tests (including evaluation of potential drug-induced liver injury) should be initiated according to the approach outlined in Table 8.

Table 8 Required Investigations and Management of Cases of Abnormal Liver Function

Laboratory value		Symptom of hepatitis or hypersensitivity [b]	Immediate action		Follow-up	
AST or ALT [a]	Total bilirubin		Consultation required	Actions	Tests	Evaluation
≥ 3 × ULN	≥ 2 × ULN [c]	NA	Hepatology consultation [d] Case must be discussed with the medical monitor ASAP	Immediate and permanent discontinuation of IP	Essential: Must have liver chemistry values and additional testing completed ASAP (Appendix F 7) or follow-up events of PHL or HL, if applicable as per Appendix F)	Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]
≥ 3 × ULN	NA	Yes				
≥ 5 × ULN	< 2 × ULN [f]	No	Case must be discussed with the medical monitor ASAP	Immediate IP discontinuation required. Permanent IP discontinuation required if follow-up tests reveal AST or ALT ≥ 3 × ULN and INR > 1.5, or ALT or AST > 5 × ULN for more than 2 weeks	Essential: Must have liver chemistry values and additional testing completed ASAP (Appendix F 7)	Hepatology consultation [d]; Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]
≥ 3 × ULN (and ≥ 2 × baseline) and < 5 × ULN	< 2 × ULN [f]	No	Discussion with medical monitor required	Temporal IP discontinuation needed for the period required for obtaining repeated liver function tests and INR. Permanent discontinuation of IP required if follow-up tests reveal AST or ALT ≥ 3 × ULN and INR > 1.5 or as deemed necessary by the investigator	Measure ALT, AST, ALP, GGT, and bilirubin (total and direct), INR, albumin in 48-72 hours. Other tests might be performed as medically indicated (at the discretion of the investigator)	If tests reveal AST or ALT ≥ 3 × ULN and INR > 1.5, then hepatology consultation and monitoring of liver chemistry values required at least twice per week until values normalise, stabilise, or return to within baseline level

[a] Note that IP should be permanently discontinued if there is a possibility of development of autoimmune hepatitis as per investigator's judgement irrespective of ALT or AST level (eg, < 3 × ULN). Participant should have a consult with a hepatologist and liver chemistry values, as well as additional tests, should be completed as soon as possible (Appendix F 7).

[b] Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include eosinophilia (≥ 5%), rash, or fever without clear alternative cause.

[c] If the participant also has ≥ 2 × ULN of ALP, the possibility of an indication of biliary obstruction should be discussed with medical monitor.

[d] Hepatologist or another appropriate specialist referral

[e] Unless an alternative monitoring schedule is agreed with by the investigator and medical monitor. Determination of stability of the liver enzyme profile is at the discretion of investigator in consultation with the hepatologist (as applicable) and medical monitor, as needed.

[f] All bilirubin values since the start of IP exposure should be checked to exclude PHL criteria (Appendix F 2). If the PHL criteria are met, IP should be immediately discontinued, and the case needs to be reported and followed-up as per guidance in Appendix F.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASAP, as soon as possible; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HL, Hy's law; INR, international normalised ratio; IP, investigational product; NA, not applicable; PHL, potential Hy's law; ULN, upper limit of normal

The criteria below make provision for the continuation of IP treatment at the discretion of the investigator.

- Participants with ALT or AST ≥ 3 × ULN (and ≥ 2 × baseline) and < 5 × ULN, total bilirubin < 2 × ULN and INR ≤ 1.5 with no symptoms of hepatitis or hypersensitivity (Table 8).

When IP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medications know to be hepatotoxic to a suitable alternative.

The following additional information should be collected:

New or updated information:

- Concomitant medications including rescue medication (paracetamol), dosages and days
- Participant's medical history:
  - History of liver disease
  - Adverse reactions to drugs
  - Allergies
  - Recent travel
- The appearance or worsening clinical symptoms of hepatitis and hypersensitivity
- Recent clinically significant hypotension with compromised cardiopulmonary function
- Results of liver imaging or liver biopsy, if done
- Any pathology reports

See Appendix F for further instructions on actions required in cases of increases in liver biochemistry and evaluation of HL.

8.2.11.2 Pregnancy

Serum pregnancy testing for β-human chorionic gonadotropin is applicable for female participants not surgically sterile and will be performed at screening as indicated in the SoA (Table 1). Urine pregnancy tests will be conducted at all dosing visits prior to IP administration as indicated in the SoA (Table 1).

Female participants who are not surgically sterile must not have a positive pregnancy test at screening as specified in inclusion criterion 6. A woman who is found to be pregnant at the screening visit will be excluded from the study and be considered a screen failure.

Urine pregnancy testing will be conducted prior to each IP administration on every woman who is not surgically sterile.

Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Procedures to be implemented if a woman becomes pregnant during the study and pregnancy reporting requirements are found in Section 8.3.10.

8.2.11.3 Urine Drug Screen

The urine drug test will be performed at the time points shown in Table 1. The drug screening includes but may not limited to amphetamine, barbiturate, cannabinoids, cocaine, methadone, methaqualone, opiate, phencyclidine, and propoxyphene.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE, SAE, and an AESI can be found in Appendix C.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs refer to Section 8.3.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from Visit 1 (including AEs related to washout period at screening), throughout the study, and including the FU period (last contact with participant).

Serious AEs will be recorded from the time the participant signs the ICF and throughout the study. All SAEs and AESIs will be recorded and reported to AstraZeneca or designee within 24 hours of awareness, as indicated in Appendix C. The investigator will submit any updated SAE data to AstraZeneca within 24 hours of it being available.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the AstraZeneca.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix C.

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to FU.

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.3 Adverse Event Data Collection

'The following variables will be collected for each AE:

- AE (verbatim)
- Date and time when the AE started and stopped
- Severity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.4 Causality Collection

The investigator should assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix C.

8.3.5 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 2.3.1 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 8.3.1 through Section 8.3.4:

- Positively-adjudicated possible or probable RPOA, SIF, primary osteonecrosis, or pathological fracture
- Infections that meet SAE or severe AE criteria*
- Anaphylactic reactions; serious or severe hypersensitivity reactions; or injection site 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 8.3.9).

*Note: A serious infection is any infection that meets the SAE criteria in CSP Appendix C 2 "Definition of Serious Adverse Event." 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.

8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/since you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP, or are considered to be clinically relevant as judged by the investigator (which may include, but not be limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the IP, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Refer to Appendix F for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representative within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it by completing the appropriate forms in the electronic data capture (EDC) system and submitting electronically to the safety team. Any follow-up information received must also be updated within the system and resubmitted within 24 hours of being made aware. SAE reporting via paper forms will only serve as backup if the EDC system were to be temporarily unavailable for any unforeseen reasons. In such cases, the electronic SAE form can be completed within the EDC system when it becomes available. This will ensure safety events are still reported within 24 hours of any site staff being made aware. The paper SAE report forms are available in the investigator site files and must be completed by the principal investigator by signing and dating the SAE Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the AstraZeneca representative.

- Email: drugsafety@mmsholdings.com
- Fax number: +1 734 468 0850

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active FU will be undertaken immediately. Investigators or other site personnel will inform the AstraZeneca representative of any FU information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the IB for MEDI7352.

For further guidance on the definition of an SAE, see Appendix C.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca or representative except for any pregnancy that is discovered before the study participant has received any IP.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

A woman who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately withdrawn from study participation. The investigator must report the pregnancy to AstraZeneca or representative as if it were an SAE (within 24 hours of learning of the pregnancy) by completing the appropriate forms in the EDC system and submitting electronically to the safety team. Pregnancy reporting via paper forms will only serve as backup if the EDC system were to be temporarily unavailable for any unforeseen reasons, as described in Section 8.3.9. The paper pregnancy notification and outcome forms are available in the investigator site files.

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca or representative via the EDC system. If paper pregnancy notification and outcome forms are used as backup, these must be completed by the principal investigator and sent via the same fax number and/or email address as for SAE reporting.

- Email: drugsafety@mmsholdings.com
- Fax number: +1 734 468 0850

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 FU information must be reported to AstraZeneca or representative (MMS) by submitting a pregnancy notification and outcome EDC report form.

8.3.10.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. 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 be considered a screen failure.

Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca or its representative via the EDC system.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel must inform the appropriate AstraZeneca representatives within **one day**, ie, immediately **but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for SAEs (Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 3 months and 20 days following the last dose.

Pregnancy in a participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose of IP until 3 months and 20 days after the last dose of IP should, if possible, be followed up and documented in the pregnancy EDC report form. The site will update the information within the EDC system and submit to AstraZeneca or representative (MMS). Consent from the partner must be obtained before the pregnancy report form is completed.

8.3.11 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel must inform the appropriate AstraZeneca representatives within **one day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or FU fatal/life-threatening) **or 5** (other serious initial and FU) **calendar days** if there is an SAE associated with the medication error (Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix C 5.

8.3.12 Management of investigational product-related toxicities

As with any biologic therapeutic agent, allergic reactions to dose administration are possible. Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions, must be immediately available when IP is administered and study site personnel must be trained to recognise and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix G.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both and at least one of the following: a) respiratory compromise or b) reduced BP or symptoms of end-organ dysfunction; or
2 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms, and/or persistent gastrointestinal symptoms; or
3 Reduced BP after exposure

Further details on the clinical criteria for defining anaphylaxis and immune complex disease are provided in Appendix G 2.

Participants will have had a preassessment (ie, vital signs and lung function) prior to IP administration. Participants should be observed for a minimum of one hour after each IP administration for the appearance of any acute drug reactions.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local laboratory at the discretion of the investigator.

8.4 Overdose

The maximal dose of IP should not be exceeded during the study. The investigator must report any overdose to an AstraZeneca representative within 24 hours of learning of the overdose by completing the appropriate forms in the EDC system and submitting electronically to the safety team. Drug overdose reporting via paper forms will only serve as backup if the EDC system were to be temporarily unavailable for any unforeseen reasons, as described for SAE reporting (Section 8.3.9). The paper forms are available in the investigator site files and must be completed by the principal investigator.

In case of a known or suspected overdose, symptomatic treatment as well as monitoring of vital functions should be performed based on the judgement of the investigator. If the overdose does not result in an AE, it should be reported to the designated individuals who receive SAE notification. The information contained therein should include study site identification, reporter identification, participant identification, IP, dose, action taken (eg, supportive measures or therapy), and any comments.

∀ An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the overdose eCRF module. Symptomatic treatment as well as monitoring of vital functions should be performed based on the judgement of the investigator.

- An overdose without associated symptoms is only reported on the overdose eCRF module.

If an overdose of an AstraZeneca IP occurs in the course of the study, the investigator or other site personnel must inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study site manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes, but is not limited to, further characterisation of any ADAs and confirmation and/or requalification of the assay, as well as additional assay development work. The results from future analysis will not be reported in the CSR.
- PD [redacted]

For further details on handling of human biological samples see Appendix D.

8.5.1 Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of MEDI7352 at the time points indicated in the SoA (Table 1). Note that participants who discontinue IP early will have their last PK sampling at the ET visit.

Drug concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the AstraZeneca and site study files but will not constitute a protocol amendment. The Institutional Review Board/Independent Ethics Committee will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Serum samples will be used to determine MEDI7352 concentration. Samples collected for analyses of MEDI7352 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples will be collected, labelled, stored, and shipped as detailed in the study site manual. The time of PK sample collection must be recorded.

8.5.1.1 Determination of Drug Concentration

Samples will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical methods used will be described in a separate bioanalytical report.

For PK analysis, it is important that the date and time of each CC injection is recorded for each participant. Only serum PK samples collected from actively treated participants will be analysed to determine the MEDI7352 concentrations. Personnel handling bioanalytical sample testing will be unblinded. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

Samples will be collected, labelled, stored, and shipped as detailed in the study site manual.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

All ADA samples will be collected prior to IP administration (on dosing days) at the time points specified in the SoA (Table 1). Note that participants who discontinue IP early will have their last ADA sampling at the ET visit. On nondosing days, ADA samples will be collected in the morning at the same time as the PK samples and the time of sample collection must be recorded.

ADA samples may also be further tested for characterisation of the ADA response (eg, neutralising antibodies).

Samples will be collected, labelled, stored, and shipped as detailed in the study site manual.

8.5.3 Pharmacodynamics

Relevant information for biomarkers including collection of blood serum and RNA is described below.

8.6 CCI

8.6.1 CCI

CCI

8.6.1.1 Pharmacodynamic Biomarkers

Plasma and serum samples for exploration of free and/or total NGF concentrations and CXCL13 concentrations will be collected at the time points specified in the SoA (Table 1). Note that participants who discontinue IP early will have their last PD sampling at the ET visit.

Samples will be analysed using a validated analytical method in compliance with AstraZeneca's standard operating procedures and analytical requirements. Instructions for sample collection, processing, storage, and shipment are provided in the study site manual.

Results from the PD biomarker analyses may be presented separately from the CSR.

8.6.1.2 CCI

CCI

[redacted]

8.6.1.3 CCI

CCI

[redacted]

8.6.1.4 CCI

CCI

[redacted]

CCI

[redacted]

8.6.2 Other Study-related Biomarker Research

Already collected samples may be analysed for different biomarkers thought to play a role in the safety and efficacy of MEDI7352 and may include, but not be limited to, proteins, metabolites, and RNA, to evaluate their association with observed clinical responses to MEDI7352.

Reuse of samples for future research is optional and requires optional agreement; participants who do not wish to have samples reused for future biomarker research may still participate in the study.

Results from the exploratory biomarker analyses will be reported separately from the CSR in reports or scientific publications.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is participant to agreement in the ICF addendum.

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Pharmacogenetic research may include evaluation of the association between DNA variation, exposure to MEDI7352, PD, safety, and efficacy.

Participation is optional; participants who do not wish to participate in the genetic research may still participate in the study. Samples can be collected at any time during the screening process after the genetic ICF is signed. If the sample is not drawn during screening for any reason, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for optional pharmacogenetics research during the study.

See Appendix E for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found in Appendix E and in the study site manual provided to the sites.

For storage and destruction of genetic samples see Appendix E.

The results of the analyses will be reported separately from the CSR in a scientific report or publication.

8.8 Medical Resource Utilisation and Health Economics

Healthcare Resource Utilisation will be assessed as an exploratory efficacy endpoint. Additional information can be found in Section 8.1.8.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Formal statistical testing is designed to preserve the overall family-wise type-error at 1-sided $\alpha = 0.025$.

Multiple Comparison Procedure-Modelling Statistical Tests

The multiple comparison stage of the Multiple Comparison Procedure-Modelling (MCP-Mod) analysis will test for the primary endpoint 'Change in the weekly average of daily NRS pain scores from baseline to Week 12' the global null hypothesis of no dose-response effect, ie, the linear contrasts of group means corresponding to each of the 6 prespecified candidate dose-response models are all identically zero.

The analysis will be performed at the 1-sided type-1 error of $\alpha = 0.025$. The minimum of the multiplicity adjusted p-values corresponding to each candidate model will be used as the basis for concluding statistical significance.

Pairwise statistical tests

For primary and key secondary endpoints, pairwise analyses will test for each dose versus placebo the null hypothesis of no treatment effect, ie, MEDI7352 dose – placebo = 0.

Pairwise testing of prespecified MEDI7352 doses versus placebo of the primary and key secondary endpoints will be performed using a sequentially rejective multiple comparison approach to ensure overall family-wise type 1 error across primary and key secondary endpoints is controlled at 1-sided $\alpha = 0.025$ (Bretz et al 2009).

The testing process will commence with the primary endpoint and testing of the key secondary endpoints will only be considered if statistical significance is demonstrated for the primary endpoint.

Further details of the multiplicity testing strategy, including the doses considered for testing, the form of the consonant component tests, and their respective weights will be prespecified in the statistical analysis plan (SAP), which will be finalised before the first interim analysis.

9.2 Sample Size Determination

Approximately 350 eligible participants will be randomly assigned to double-blind treatment with one of 4 dose levels of MEDI7352 or placebo. Recruitment will continue until the planned unconditional power of the study is achieved (ie, when statistical information equivalent to 255 participants completing the treatment period is reached or approximately 350 randomised participants, whichever is sooner. The statistical information will be calculated based upon ongoing blinded study data. Further details will be given in the Statistical Analysis Plan.

With statistical information equivalent to 255 evaluable participants, the study will have greater than 90% power to detect a statistically significant (at overall 1-sided $\alpha = 0.025$) dose-response relationship using a MCP-Mod approach for the primary endpoint: Change in the weekly average of daily NRS pain scores from baseline to Week 12. This assumes that the true Week 12 placebo-corrected change from baseline difference at the CCI dose is 1.5, the true dose-response follows a maximum response (Emax) relationship with a dose that produces half of the E_{max} (ED_{50}) = CCI and a SD = 2.4.

The 6 candidate dose response models incorporated into the MCP-Mod test were chosen to reflect potential convex, linear, and concave dose-response relationships and are as follows:

- Three convex E_{max} models with increasing ED_{50}: CCI
- One model linear in dose
- Two concave exponential models defined by 10% and 25% of the maximum drug effect at CCI

The above calculations were performed using the software R and the R-package 'DoseFinding' [https://cran.r-project.org/web/packages/DoseFinding/DoseFinding.pdf]

9.3 Populations for Analyses

The following populations are defined (Table 9):

Table 9 Populations for Analysis

Population/Analysis set	Description
Screening set	This set includes all participants who provide informed consent and/or assent and provide demographic and/or baseline screening assessments, regardless of the participant's randomisation and treatment status in the study.

Table 9 Populations for Analysis

Population/Analysis set	Description
Full analysis set	This set will be used for all efficacy analyses, and it is defined according to the intent-to-treat principle as including all randomised participants.
PK set	This set includes all participants who received at least one dose of double-blind IP per the protocol for whom any postbaseline PK data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses.
Safety set	This set will include all participants who receive at least one dose of double-blind IP

IP, investigational product; PK, pharmacokinetics

9.4 Statistical Analyses

The SAP will be finalised before the first interim analysis and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Formal statistical analysis will be undertaken for the primary and key secondary efficacy endpoints, with the aim of maintaining overall family-wise type-1 error at 5% level (2-sided) or, equivalently, at 2.5% level (1-sided). The analysis of any remaining endpoints (including other efficacy, safety, and those in Section 9.4.4) will be for estimation purposes.

Generally, for each endpoint, baseline is defined as the latest assessment prior to the first dose of randomised treatment. For the primary endpoint (change in weekly average of daily NRS pain scores), the baseline is defined as the mean of daily NRS pain scores recorded during the 7-day period immediately prior to randomisation, ie, Day -7 to Day -1, inclusive. Details of 'analysis visit windows' used for statistical reporting will be included in the SAP.

9.4.2 Efficacy

All efficacy variables will be summarised 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 or unevaluable data at a key analysis time-point (Weeks 4, 8, and 12) then results will also be tabulated according to single imputation 'last-observation-carried forward' (LOCF) or 'baseline-observation-carried-forward' (BOCF), depending upon the intercurrent event leading to missing or unevaluable data. The presentation of single

imputed data is intended as an approximation to the approach taken for the formal analyses and also to allow historical comparison.

9.4.2.1 Primary Endpoint

An 'attributable 4' estimand strategy will be adopted for primary endpoint data missing or affected by any of the following 4 intercurrent events:

- ∀ Discontinuation due to lack of efficacy, or an AE
- ∀ Discontinuation due to other reasons such as loss to FU or external circumstances
- ∀ Taking prohibited pain medication during the treatment period that may confound the effect of initially randomised treatment on the primary endpoint
- ∀ Taking excessive permitted rescue medication that may confound the effect of initially randomised treatment on the primary endpoint

The rationale for choosing the attributable estimand (Darken et al 2020) is because if a participant does not receive treatment for the duration of the study (due to an AE or lack of efficacy), or switches to a prohibited therapy, or uses excessive rescue medication, he/she is considered to be a treatment failure and so handled with a composite estimand strategy, while a hypothetical estimand strategy is used for intercurrent events not considered to be related to randomised treatment such as discontinuation due to 'other reasons'.

Note that it is expected that participants would be switched to alternative treatments following discontinuation of randomised treatment or withdrawal, which would confound any assessment of efficacy attributable to randomised treatment; therefore, retrieved dropout information will not be collected.

Primary endpoint data missing due to discontinuation due to lack of efficacy or an AE will be imputed assuming an unfavourable outcome. Data affected by prohibited or excessive rescue medication will be set to missing and imputed assuming an unfavourable outcome. For these intercurrent events, a return-to-baseline multiple imputation approach will be used which assumes that any treatment effects observed prior to the intercurrent event are washed out, such that the mean effect at the end of the study among such participants is the same as that at baseline. This seems reasonable where participants enter the study with a chronic level of moderate-to-severe pain and the treatment effect is expected to be reversible.

Primary endpoint data missing due to other reasons will be imputed using a "missing-at-random" multiple imputation approach.

Further details of the multiple imputation models and number of imputations will be included in the SAP.

The main statistical analysis of the primary efficacy endpoint at Week 12 will use the MCP-Mod approach, which is a well-established statistical methodology for establishing both the existence of a dose response and modelling the underlying dose-response relationship (EMA 2013, FDA 2015).

There are 2 steps to MCP-Mod:

- ∀ The 'MCP' step is a rigorous method to establish presence of a dose response while protecting the type 1 error and, if the dose-response relationship is statistically significant, then
- ∀ The 'Mod' step estimates the dose response function and associated model parameters, such as ED_{50} in the case of E_{max} relationship.

The MCP test will use linear contrasts corresponding to the 6 candidate models described in Section 9.2. 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 KL grade. 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 dose-response model (including the same covariates as the ANCOVA model) from which various estimates will be derived (together with confidence intervals) of parameters of interest such as ED_{50}, 90% of the E_{max} (ED_{90}), dose to achieve selected target effects, and model estimates of the treatment effect at doses studied.

Pairwise testing will be performed using the multiple comparison approach described in Section 9.1 based upon the same ANCOVA model as used for the MCP-Mod analyses.

For each analysis, the testing and estimation will be based upon Rubin's method of combination of the repeated analyses of complete multiply-imputed datasets.

9.4.2.2 Secondary Endpoint(s)

The same analysis approach as for the primary endpoints will be applied to the analysis of the key secondary endpoints WOMAC pain, WOMAC physical function, and PGA of OA.

Other continuous secondary endpoints will be analysed by single BOCF/LOCF imputation approaches, where LOCF is used for intercurrent event discontinuation due to other reasons and BOCF for other intercurrent events.

For binary (responder-type) secondary endpoints, a logistic regression analysis will be performed with the same covariates as for the respective continuous endpoint. A mixed BOCF/LOCF imputation will be used for missing or unevaluable data. In this analysis, LOCF

would be used to assign response for participants with intercurrent event discontinuation due to other reasons and BOCF imputation (ie, a participant would be a nonresponder) otherwise.

9.4.2.3 CCI

CCI

9.4.3 Safety Analyses

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

The baseline value for statistical analysis is generally the last assessment immediately prior to administration of the first dose of IP. Details are described in the SAP.

9.4.3.1 Adverse events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs will be presented for each treatment group by system organ class and/or preferred term covering the number and percentage of participants reporting at least one event and number of events where appropriate.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of IP through the last visit, or
- AEs starting prior to the start of IP administration but increasing in severity or relationship at the time of, or following, the start of IP through the last visit

An overview of AEs will be presented for each treatment group and will include the number and percentage of participants with any AE, AEs with outcome of death, SAEs, AEs leading to discontinuation of IP, and AEs leading to withdrawal from study, as well as the number of individual occurrences in those categories. Separate AE tables will be provided taking into consideration severity, relationship to IP, death, SAEs, AEs leading to discontinuation of IP, and AESI.

An additional table will present the number and percentage of participants with most common AEs. Most common AEs will be defined in the SAP.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IP.

The incidence of participants with adjudicated events of RPOA (type 1 and 2), SIF, primary osteonecrosis, or pathological fracture will be listed by the number of participants treated per treatment group and by differences between MEDI7352 and placebo.

The incidence of cases of joint replacement surgery will be listed by the number of participants per treatment group and by differences between MEDI7352 and placebo.

Participant listings of AESIs and also AEs, SAEs, and AEs causing discontinuation of IP will be generated.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 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 participants with clinical laboratory values categorised 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 be 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.

Elevation in liver parameters for assessment of HL will be collected and reported appropriately if potential cases have been identified during the course of the study.

A frequency table for urinalysis will present the number of participants reporting at least one treatment emergent increase in baseline category. A shift table for urinalysis will present the baseline assessment against the maximum on-treatment category.

9.4.3.3 Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for (n, mean, SD, minimum, Q1, median, Q3, and maximum) will be presented for systolic BP, diastolic BP, pulse rate, orthostatic BP changes, respiratory rate, and temperature.

For each scheduled postbaseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

In addition, the incidence of orthostatic hypotension and mean changes in postural BP will be summarised.

9.4.3.4 12-Lead Electrocardiogram

Results of the safety ECGs, including normal/abnormal and specific findings will be listed for each participant.

9.4.3.5 Physical and Neurological Examination Findings

Physical and neurological examination findings will be listed for all participants. A summary of the final assessment across all neurological evaluations will be provided for each participant.

9.4.3.6 Other Safety Endpoint(s)

Findings from other safety assessments (TNSn and injection site reactions) will be listed and may be summarised if warranted.

The SAS scores will be summarised by treatment group for the total number of symptoms reported and the total impact score. The summary will be presented by visit and will include the change from baseline.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

Pharmacokinetics of MEDI7352 will be characterised with a population PK model. MEDI7352 trough concentration (C_{trough}) will be summarised descriptively.

Statistical analyses of PK parameters will be outlined in the SAP.

The population PK analysis will be presented separately from the CSR.

9.4.4.2 Pharmacodynamics

The PD variables (free and/or total NGF, CXCL13) will be summarised using descriptive statistics. The association between PD variables and efficacy endpoints will be explored. Further details will be included in the SAP.

The PD analyses will be presented separately from the CSR.

9.4.4.3 Pharmacogenetics

Analysis of optional pharmacogenetics data will be described in a separate analysis plan. Results will be reported in a separate pharmacogenetics report.

9.4.4.4 CCI

CCI [redacted]

9.4.4.5 Immunogenicity

Immunogenicity results will be analysed descriptively by summarising the number and percentage of participants who develop detectable anti-MEDI7352 antibodies. ADA titre will also be determined. The effects of ADAs on PK, PD, safety and efficacy will be explored.

9.4.5 CCI

CCI

9.4.6 Sensitivity Analysis

For primary and key secondary endpoints, sensitivity analyses of the attributable estimand will explore different 'missing not at random' imputation approaches other than return-to-baseline.

Supplementary analyses of the primary and key secondary endpoints may be conducted to provide additional insights into the understanding of the treatment effect.

9.5 Interim Analyses

The study incorporates 2 interim analyses: (1) a futility analysis will take place when approximately 25% of participants are evaluable for the primary endpoint; this analysis will assess the likely success of the study outcome and will enable the sponsor to make a go/no-go decision regarding continuation of the study; and (2) an interim analysis of efficacy data will take place when approximately 50% of participants are evaluable for the primary endpoint; this analysis will enable the sponsor to plan future project-related activities, but without making any changes to the current study.

No alpha adjustment is required for the interim analyses because early stopping for efficacy is not a feature of the study design.

Unblinded personnel who are not otherwise involved in the study will prepare the data for review by the Independent Efficacy Review Group, who are themselves independent of the day-to-day study activities. The study team will remain blinded to the results of the interim analyses for the duration of the study. Firewalls will be put in place to ensure that information is not inadvertently disseminated.

The interim SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committees

For additional details relevant to the data monitoring committees, refer to Appendix B 5

∀ Data and Safety Monitoring Board: The DSMB will conduct periodic reviews of safety data from all enrolled participants throughout the clinical study. The DSMB will make

recommendations to the sponsor, based on these data, on the future conduct of the clinical study and in particular on whether to continue, terminate, or modify the clinical study.

- ∀ Independent Efficacy Review Group: This group will be independent of the study team and will review, interpret, and adjudicate on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes.
- ∀ RPOA-AC: The role of this committee is to independently review, interpret, and adjudicate possible or probable joint safety events including but not limited to RPOA, SIF, primary osteonecrosis, or pathological fracture cases that are experienced by the study participants. The RPOA-AC will review and adjudicate all treatment-emergent joint safety events that meet SAE or severe AE criteria or which led to joint replacement or other arthroplasty procedures.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Clinical Study Protocol Signatures

SPONSOR SIGNATURES

A Randomised, Double-blind, Placebo-controlled, Dose-response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

Global Amendment 3 to Protocol D5680C00003

This Clinical Study Protocol and all Amendments/Addendums to the Protocol have been subjected to an internal AstraZeneca peer review.

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

Sponsor or affiliate Research and Development site representative

PPD

PPD

Date
(Day Month Year)

Neuroscience, Biopharmaceuticals Research and Development
AstraZeneca
Aaron Klug Building, Granta Park
Cambridge CB21 6GH
United Kingdom
Tel: PPD

SPONSOR SIGNATURES

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PPD

PPD

Date
(Day Month Year)

, Clinical Development,
Neuroscience
Neuroscience, Biopharmaceuticals Research and Development
AstraZeneca
Aaron Klug Building, Granta Park
Cambridge CB21 6GH
United Kingdom
Tel: PPD

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Sponsor or affiliate Research and Development site representative

PPD

PPD

Date
(Day Month Year)

, Neuroscience
Neuroscience, Biopharmaceuticals Research and Development
AstraZeneca
Aaron Klug Building, Granta Park
Cambridge CB21 6GH
United Kingdom
Tel: PPD

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Sponsor or affiliate Research and Development site representative

PPD

PPD

Date
(Day Month Year)

Director Neuroscience Physician
Neuroscience, Biopharmaceuticals Research and Development
AstraZeneca
Aaron Klug Building, Granta Park
Cambridge CB21 6GH
United Kingdom
Tel: PPD

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

Sponsor or affiliate Research and Development site representative

PPD

PPD

Date
(Day Month Year)

Empiridat Ltd
Quetta
Jubilee Road
Worth
Deal CT14 0DS
United Kingdom
Tel: PPD

SIGNATURE OF NATIONAL COORDINATING INVESTIGATOR

A Randomised, Double-blind, Placebo-controlled, Dose-response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

Global Amendment 3 to Protocol D5680C00003

This Clinical Study Protocol and all Amendments/Addendums to the Protocol have been subjected to external peer review.

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

Signature: PPD

PPD
Chapel Allerton Hospital
Chapeltown Road
LS7 4SA

Tel: PPD

Date
(Day Month Year)

Appendix B Regulatory, Ethical, and Study Oversight Considerations

B 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/ IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a serious adverse event (SAE) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product (IP) under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

B 2 Financial Disclosure

Investigators and subinvestigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study. Study completion is defined as the date when the last participant completes protocol-defined activities.

B 3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be consented/reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant’s legally authorised representative.

A participant who is rescreened is required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or their future use and may withdraw their consent at any time and for any reason during the retention period.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain the objectives of the exploratory research to each participant. Participants will be told that they

are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The participant will give a separate agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will indicate this in the ICF. If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples have been analysed already at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

All participants will be asked to donate a sample for the Genomics Initiative (see Section 8.7 and Appendix E for additional information regarding informed consent). For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the clinical study protocol (CSP) and must provide informed consent for the Genomics Initiative sampling and analyses. If a participant declines participation in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the participant and he/she will not be excluded from other aspects of the study.

B 4 Data Protection

Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

B 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be appointed and will report to AstraZeneca. The DSMB will be responsible for safeguarding the interests of the participants in the study by assessing the safety of the IP during the study. The DSMB will have access to the individual treatment codes and be able to merge these with the collected study data while the study is ongoing if necessary.

The DSMB will make recommendations to the sponsor, based on these data, on the future conduct of the trial and in particular on whether to continue, terminate, or modify the study. To do so, the DSMB may make their recommendations on the basis of access to unblinded data at both the participant and treatment group level. Along with a recommendation, the committee will provide sufficient contextual information such that the sponsor can determine whether and how to implement the recommendation.

A DSMB charter will be prepared to detail committee membership and precise roles, responsibilities, and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with AstraZeneca. The DSMB will ensure that the study meets high standards of ethics and patient safety.

Independent Efficacy Review Group

The role of the Independent Efficacy Review Group is to independently review, interpret and adjudicate on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes. The group will make recommendations to the study team, based on these analyses, on the future conduct of the trial and in particular on whether to continue, terminate or modify the study. To do so, the group will make their recommendations on the basis of access to unblinded data at both the participant and treatment group level. Along with a recommendation, the group will provide sufficient contextual information such that the study team can determine whether and how to implement the recommendation.

The Independent Efficacy Review Group will consist of sponsor personnel who are independent of the study team.

The membership, responsibilities, and procedures applicable to the Independent Efficacy Review Group will be detailed in its charter.

Rapidly Progressive Osteoarthritis Adjudication Committee

The role of the Rapidly Progressive Osteoarthritis Adjudication Committee (RPOA-AC) is to independently review, interpret, and adjudicate possible or probable joint safety events including but not limited to RPOA, SIF, primary osteonecrosis, or pathological fracture cases that are experienced by the study participants. The RPOA-AC will review and adjudicate all joint safety events that meet SAE or severe AE criteria or AEs that led to joint replacement or other arthroplasty procedures to determine whether or not they meet accepted diagnostic criteria. Joint safety events will be identified preliminarily by the investigators, and also by AstraZeneca/sponsor personnel or during the RPOA-AC process as specified in the committee's charter. The RPOA-AC member/s will not have access to individual treatment codes for any participant and will remain blinded to treatment throughout the study duration.

Causality assessments will also be made by the RPOA-AC in a blinded fashion. The committee will not possess governance authority, but its adjudication and opinion will be considered in relation to prespecified stopping criteria in the protocols

The objectives for performing the adjudication of cases from study D5680C0003 are to:

- ∀ Gain the adjudicators' agreement on the definition of possible or probable RPOA (type 1 and type 2), SIF, primary osteonecrosis, or pathological fracture cases.
- ∀ Agree on a diagnosis for cases based on available X-ray, magnetic resonance imaging, and clinical data
- ∀ Receive a collective opinion on the attribution [causality] of the diagnosis of cases based on blinded treatment.

The RPOA-AC should comprise no less than 3 physicians from various specialities who have expertise in the diagnosis and treatment of RPOA and in the medical aspects of clinical trials in osteoarthritis. The Investigator's Manual or other investigator material will specify the information to be collected for potential RPOA events.

The precise responsibilities and procedures applicable for RPOA-AC will be detailed in its charter.

B 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com, http://www.clinicaltrials.gov, and https://www.clinicaltrialsregister.eu as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

B 7 Data Quality Assurance

- ∀ All participant data relating to the study will be recorded in the electronic case report form (eCRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- ∀ The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- ∀ The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- ∀ Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

- ∀ The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- ∀ The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- ∀ Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- ∀ Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

B 8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in monitoring plan.

B 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- ∀ Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- ∀ Inadequate recruitment of participants by the investigator
- ∀ Discontinuation of further IP development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant treatment and/or follow-up.

B 10 Publication Policy

The results of this study may be published or presented at scientific meetings. Publications developed and managed by the investigator will be shared with the sponsor for review and approval before submission. This allows the sponsor to review the publication for accuracy and to ensure any proprietary information is protected.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix C Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

C 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no investigational product (IP) has been administered.

C 2 Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for malignant tumours reported during a study should generally be assessed as **serious** AEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, 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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of important medical events that require judgement to determine if they are to be considered an SAE:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix C 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix C 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix C 2.

C 3 Definition of Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and collecting 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. Adverse events of special interest are described in Section 8.3.5.

C 4 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

C 5 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca IP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error;

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology/Randomisation and Trial Supply Management [IRT/RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- ∀ Errors related to or resulting from IRT/RTSM errors - including those which lead to one of the above listed events that would otherwise have been a medication error
- ∀ Participant accidentally missed drug dose(s), eg, forgot to take medication
- ∀ Accidental overdose (will be captured as an overdose)
- ∀ Participant failed to return unused medication or empty packaging
- ∀ Errors related to background and rescue medication, or standard-of-care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix D Handling of Human Biological Samples

D 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their life cycle.

The investigator at each study site keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

D 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- ∀ Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca.
- ∀ Ensures that biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- ∀ Ensures that the participant and AstraZeneca are informed about the sample disposal.
- ∀ Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.

D 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A infectious substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B infectious substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- To be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not participant to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix E Optional Genomics Initiative Sample

E 1 Use/Analysis of DNA

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Board/Independent Ethics Committee (IRB/IEC) allow, a blood sample will be collected for DNA analysis from consenting participants.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to a better understanding and diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.

The results of genetic analyses may be reported in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

E 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All participants will be asked to participate in this genetic research. Participation is voluntary, and if a participant declines to participate, there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the clinical study protocol (CSP) and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- ∀ Previous allogeneic bone marrow transplant
- ∀ Non–leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection
- ∀ No Genomics Initiative samples to be collected from healthy volunteers and paediatric participants.

Withdrawal of Consent for Genetic Research

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

A 6 mL K2 ethylenediaminetetraacetic acid blood sample will be collected for the Genomics Initiative sample.

The blood sample for this genetic research will be obtained from the participants at Visit 1 specified in the schedule of assessments (Table 1). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an adverse event (AE). If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for

analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix B.

Informed Consent

The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that he/she may freely withdrawal from the genetic aspect of the study at any time.

Subject Data Protection

AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, participant's family members, or participant's general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of participants 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. A statistical analysis plan may be prepared where appropriate.

Appendix F Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

F 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 product (IP).

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

F 2 Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or ALT ≥ 3 × upper limit of normal (ULN) **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

F 3 Identification of Potential Hy's Law Cases

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

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

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met; where this is the case the investigator will:

- Notify the AstraZeneca representative.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory electronic case report form (eCRF) 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 participant meets PHL criteria (see Appendix F 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local Laboratories Being Used:

The investigator will, without delay, review each new laboratory report, and if the identification criteria are met, the investigator will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Appendix F 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

F 4 Follow-up

F 4.1 Potential Hy's Law Criteria not Met

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

- ∀ Inform the AstraZeneca representative that the participant has not met PHL criteria.
- ∀ Perform follow-up of subsequent laboratory results according to the guidance provided in the clinical study protocol (CSP).

F 4.2 Potential Hy's Law Criteria Met

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

- ∀ Notify the AstraZeneca representative who will then inform the central study team.
- ∀ Within one day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- ∀ For participants that met PHL criteria prior to starting IP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- ∀ The study physician contacts the investigator to provide guidance, discuss, and agree on an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data.
- ∀ Subsequent to this contact the investigator will:
  - # Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
  - # Complete follow-up SAE form as required.
  - # Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician. This includes deciding which tests available in the HL lab kit should be used.
  - # Complete the 3 liver eCRF modules as information becomes available.

[#] A **'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

F 5 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.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

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

Where 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 whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

- Send updated SAE (report term ‘Hy’s Law’) according to AstraZeneca standard processes.
  - The ‘medically important’ serious criterion should be used if no other serious criteria 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 15 calendar days 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:

- Provide any further update to the previously submitted SAE of PHL, (report term now ‘HL case’) ensuring causality assessment is related to IP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report

following the CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

F 6 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on IP and has already met PHL criteria at a previous on-IP visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Did the participant meet PHL criteria prior to starting IP and at their first on-IP visit?

If **No**: follow the process described in Appendix F 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met

- ∀ If there is no significant change no action is required
- ∀ If there is a significant change[#] follow the process described in Appendix F 4.2 for reporting PHL as an SAE

[#] **A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

F 7 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests that are recommended when using a central laboratory.

Some of the tests may also be considered for use with local laboratories that have the respective testing capabilities. Any test results need to be recorded in the CRF.

Table F10 Lab Kit for Central Laboratories for Investigations and Management of Cases of Abnormal Liver Function (including Hy's Law cases)

Description	Test
Additional standard chemistry and coagulation tests	GGT
	LDH
	Prothrombin time
	INR
Viral hepatitis	IgM anti-HAV
	HBsAg
	IgM and IgG anti-HBc
	HBV DNA [a]
	IgG anti-HCV
	HCV RNA [b]
	IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV
	IgM & IgG anti-HSV
	IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA)
	Anti-Liver/Kidney Microsomal Ab (Anti-LKM)
	Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin
	Ceruloplasmin
	Iron
	Ferritin
	Transferrin [c]
	Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] CD-transferrin and transferrin are not available in China.

F 8 References

Aithal et al, 2011

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, **et al**. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011 Jun;89(6):806-15.

FDA Guidance for Industry, July 2009

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix G Anaphylaxis: Definition, Signs, Symptoms, and Management

G 1 Introduction

As with any biologic therapeutic agent, allergic reactions to dose administration are possible. The World Health Organisation has categorised anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (immunoglobulin E [IgE]-mediated and non-IgE-mediated [eg, immunoglobulin G and immune complex-mediated]) and nonimmunologic (Johansson et al 2004). The clinical criteria for defining anaphylaxis for this study are listed in Section G 2 of this Appendix. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Section G 3 of this Appendix. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognise and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample for serum tryptase should be collected as soon as possible after the event, at 90 ± 30 minutes after the event, and at discharge; analysis for serum tryptase will be performed at a local laboratory. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the investigator.

G 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalised hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
   - Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia).
   - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
   - Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula).
   - Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

- Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, and incontinence).
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3 Reduced BP after exposure to known allergen for that participant (minutes to several hours). For adults, this corresponds to a systolic BP of less than 90 mm Hg or a greater than 30% decrease from that participant's baseline.

Immune Complex Disease

Immune complex disease or hypersensitivity type III is evoked by the deposition of antigen-antibody or antigen antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness, and nephritis are common.

G 3 Signs and Symptoms and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multisystem allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal oedema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhoea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhoea, abdominal cramps, and bloating
- Light-headedness
- Headache
- Uterine cramps
- Generalised warmth

G 4 Management of Acute Anaphylaxis

G 4.1 Immediate Intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation.

2 Administer epinephrine intramuscularly every 5 to 15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock, and unconsciousness.

G 4.2 Possibly Appropriate, Subsequent Measures Depending on Response to Epinephrine

(a) Place participant in recumbent position and elevate lower extremities

(b) Establish and maintain airway

(c) Administer oxygen

(d) Establish venous access

(e) Normal saline IV for fluid replacement

G 4.3 Specific Measures to Consider After Epinephrine Injections, Where Appropriate

(a) Consider epinephrine infusion

(b) Consider H1 and H2 antihistamines

(c) Consider nebulised β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine

(d) Consider systemic corticosteroids

(e) Consider vasopressor (eg, dopamine)

(f) Consider glucagon for participant taking β-blocker

(g) Consider atropine for symptomatic bradycardia

(h) Consider transportation to an emergency department or an intensive care facility

(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary

Adapted from Kemp et al 2008.

Appendix H Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor. Instructions on how to perform these procedures will be provided at the time of implementation.

H 1 Reconsent of Study Subjects During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Consent/reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections H 2 to H 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (Note: In the case of verbal reconsent, the informed consent form should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified healthcare provider (HCP) from the study site or third-party vendor (TPV) service will visit the participant's home or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol. If applicable, assessments will be performed according to a revised schedule of assessments (SoA).

H 3 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events and concomitant medications to be reported

and documented. If applicable, safety procedures and blood sample collection will be performed according to a revised SoA.

H 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service or by the participants themselves (eg, numerical rating scale daily pain score, daily sleep interference score, rescue medicine) via appropriate means.

Appendix I Summary of Imaging Assessments

Imaging assessments to be performed during the study are shown in Table I11, and the timing of these assessments are described in Table I12.

Table I11 Imaging Assessments to be Performed During the Study

Joints/indications	X-ray (plain radiographs)	MRI
Knee (both) [a]	E and S	E and S
Hip (both) [a]	E and S	For joints with KL grade 3 or more
Shoulders (both)	E and S	When further clarification of imaging findings needed
Other joints:		
Any major joint with KL grade 3 or more		E and S
As clinically indicated (CS worsening of OA symptoms or newly occurred CS symptoms)	S (all joints except for hip joints with KL grade ≥ 3 [b])	S (knees and/or major joints with KL grade ≥ 3)
Other indications:		
When the central readers or RPOA-AC need to further clarify imaging finding	S	S
At screening for other major joints (elbows, wrists, and ankles) exhibiting signs or symptoms associated with OA	E and S	N/A

[a] Scheduled X-ray at Week 32 is required for hips and knees only.

[b] Note that X-ray for hip joints with a KL grade at screening ≥ 3 might be also performed if deemed necessary by the investigators or RPOA-AC.

CS, clinically significant; E, eligibility; KL, Kellgren and Lawrence; MRI, magnetic resonance imaging; OA, osteoarthritis; S, safety; RPOA-AC, Rapidly Progressive Osteoarthritis Adjudication Committee

Table I12 Schedule of Assessments - Imaging

Imaging	Knee	Hip	Shoulder	Other joints	Other time points
X-ray	At screening and at Week 32 (or FU clinic Visit 2 for participants who discontinued IP early) and as clinically indicated during the study	At screening and at Week 32 (or FU clinic Visit 2 for participants who discontinued IP early) and as clinically indicated during the study [a]	At screening and as clinically indicated during the study	At screening for other major joints (elbows, wrists, and ankles) exhibiting signs or symptoms associated with OA at screening; for any joints as clinically indicated during the study	At any time point during the study when deemed necessary by the investigator or central reader or RPOA-AC
MRI	Both knee joints at screening and as clinically indicated during the study	Joints with KL grade 3 or more at screening and as clinically indicated during the study	As clinically indicated during the study	At screening and as clinically indicated for joints with KL grade ≥ 3 during the study	When deemed necessary by central radiology readers or RPOA-AC

[a] Note that imaging via MRI should be the first step in case of joint safety events in hip joint with KL grade 3 or more.

FU, follow-up; IP, investigational product; KL, Kellgren and Lawrence grade, MRI, magnetic resonance imaging; N/A, not applicable; OA, osteoarthritis; RPOA-AC, Rapidly Progressive Osteoarthritis Adjudication Committee

Appendix J 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:

Nonsterilised 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 3 months and 20 days after the last administration of investigational product (IP). As male condom and spermicide are not considered to constitute a highly effective contraception method, female partners of male study participants must also use a highly effective method of contraception for the duration of the treatment period and for 3 months and 20 days after the last administration of IP. 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 J13.

Table J13 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method.

[b] With appropriate postvasectomy 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 3 months and 20 days after the last IP administration and if it is the preferred and usual lifestyle of the participant.

[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).

IUS, intrauterine system

Appendix K Half-lives of Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

Table K14 Half-lives of NSAIDs and Other Analgesics

Analgesic	Half-life (hours)	Minimum washout period
Azapropazone	15.0	4 days
Bromfenac	1.3-3.1	2 days
Capsaicin (cream, ointments, patches)	2.0	2 days
Carprofen	12.0	3 days
Celecoxib	11.0	3 days
Codeine	3.5	2 days
Diclofenac	1.1	2 days
Diclofenac gels	1.9	2 days
Diclofenac/misoprostol	2.4-9.0	2 days
Diflusinal	13.0	3 days
Dipyrone	2.0-5.0	2 days
Etodolac	6.0	2 days
Fenbufen	11.0	3 days
Fenoprofen	2.5	2 days
Flufenamic acid	1.4	2 days
Flurbiprofen	3.8	2 days
Ibuprofen	2.1	2 days
Indomethacin	4.6	2 days
Ketoprofen	1.8	2 days
Ketorolac	4.0-9.0	2 days
Lidocaine patch or EMLA (lidocaine/prilocaine)	2.0	2 days
Meclofenamate	2.0-4.0	2 days
Mefenamic acid	2.0	2 days
Meloxicam	16.0-20.0	5 days
Meperidine	3.7	2 days
Mexiletine	6.0-17.0	4 days
Nabumetone	26.0	6 days
Naproxen	14.0	3 days
Oxaprofen	40.0-50.0	11 days
Oxaprozin	58.0	13 days
Phenylbutazone	68.0	15 days

Table K14 Half-lives of NSAIDs and Other Analgesics

Analgesic	Half-life (hours)	Minimum washout period
Piroxicam	57.0	12 days
Pirprofen	3.8	2 days
Salicylates	2.0-15.0	4 days
Sulindac	14.0	3 days
Suprofen	2.5	2 days
Tenoxicam	60.0	13 days
Tiaprofenic acid	3.0	2 days
Tolmetin	1.0	2 days
Tramadol	5.9	2 days

Appendix L Abbreviations

Abbreviation or special term	Explanation
ABPM	ambulatory blood pressure monitoring
ACPA	anti-citrullinated protein antibodies
ADA	antidrug antibody
AE(s)	adverse event(s)
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
ANCOVA	analysis of covariance
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase/transaminase
BOCF	baseline-observation-carried-forward
BP	blood pressure
$C_{average}$	average observed drug concentration over the dosing interval
CFR	Code of Federal Regulations
C_{max}	maximum (peak) observed drug concentration
COVID-19	Coronavirus disease 2019
COX-2	cyclooxygenase-2
CRP	C-reactive protein
CSP	clinical study protocol
CSR	clinical study report
CCI	[redacted]
DILI	drug induced liver injury
DMARD(s)	disease-modifying antirheumatic drugs
DSIS	Daily Sleep Interference Scale
DSMB	Data and Safety Monitoring Board
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment
eCRF	electronic case report form
ED_{50}	half of the E_{max}
EDC	electronic data capture
E_{max}	maximum response
EOT	end-of-treatment
ePRO	electronic patient-reported outcome

Abbreviation or special term	Explanation
ET	early termination
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
FU	follow-up (as adjective)
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care provider
CCI	[redacted]
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's Law
IB	Investigator's Brochure
IATA	International Airline Transportation Associations
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
INR	international normalised ratio
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KL	Kellgren and Lawrence
LOCF	last-observation-carried-forward
LVEF	left ventricular ejection fraction
MAD	multiple-ascending dose
MCP-Mod	multiple comparison procedure-modelling
CCI	[redacted]
MRI	magnetic resonance imaging
CCI	[redacted]
NGF	nerve growth factor
NRS	numerical rating scale

Abbreviation or special term	Explanation
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis
OMERACT-OARSI	Outcome Measures in Rheumatology-Osteoarthritis Research Society International
OTC	over the counter
PD	pharmacodynamics
PDN	painful diabetic neuropathy
PEF	peak expiratory flow
PGA	Patient's Global Assessment
PHL	Potential Hy's Law
PK	pharmacokinetic(s)
Q2W	every 2 weeks
QTcF	corrected QT interval by Fredericia
RA	rheumatoid arthritis
RBC(s)	red blood cell(s)
RNA	ribonucleic acid
RPOA	rapidly progressive osteoarthritis
RPOA-1/RPOA-2	rapidly progressive osteoarthritis type 1/ rapidly progressive osteoarthritis type 2
RPOA-AC	Rapidly Progressive Osteoarthritis Adjudication Committee
RTSM	Randomisation and Trial Supply Management
SAD	single-ascending dose
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Survey of Autonomic Symptoms
C CI	[redacted]
scFv	single chain variable domain fragment
SD	standard deviation
CCI	[redacted]
SIF	subchondral insufficiency fracture
SoA	schedule of assessments
SUD	substance use disorders
SUSAR	serious adverse reactions
TB	tuberculosis
TBL	total bilirubin
TEAE	treatment-emergent adverse event

Abbreviation or special term	Explanation
TNF	tumour necrosis factor
TNFα	tumour necrosis factor-alpha
TNFR2	TNF receptor 2
TNSn	Total Neuropathy Score-nurse
TPV	third-party vendor
ULN	upper limit of normal
WFI	water for injection
WOMAC	Western Ontario and McMaster Universities Osteoarthritis
CCI [redacted]	[redacted]

Appendix M Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is presented on the following pages.

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
1.1 Synopsis (Number of Subjects)	This is multinational, multicentre, interventional study in which approximately 300 eligible participants will be randomly assigned to the IPs (one of 4 dose levels of MEDI7352 or placebo) to ensure that approximately 255 participants complete the treatment period.	This is a multinational, multicentre, interventional study in which approximately 350~~300~~ eligible participants will be randomly assigned to the IPs (one of 4 dose levels of MEDI7352 or placebo) ~~to ensure that approximately 255 participants complete the treatment period~~.	To increase the study sample size and ensure enough participants are recruited to achieve adequate study power.	Substantial
1.1 Synopsis (Sample Size Determination)	Approximately 300 eligible participants will be randomly assigned to IPs (MEDI7352 or placebo) to ensure that approximately 255 participants complete the treatment period. With 255 evaluable participants, the study will have greater than 90% power to detect a statistically significant (at overall 1 sided α = 0.025) dose-response relationship using a multiple comparison procedure-modelling (MCP-Mod) approach for the primary endpoint 'Change in the weekly average of daily NRS pain scores from baseline to Week 12'. This assumes that the true Week 12 placebo-corrected change from baseline difference at the CCI dose is 1.5, and the true dose-response follows a maximum response (Emax) relationship with a dose that produces half of the Emax (ED50) = CCI and a standard deviation (SD) = 2.4.	Approximately 350~~300~~ eligible participants will be randomly assigned to IPs (MEDI7352 or placebo) ~~to ensure that approximately 255 participants complete the treatment period~~. Recruitment will continue until the planned power of the study is achieved (ie, when statistical information equivalent to 255 participants completing the treatment period is reached) or approximately 350 randomised patients, whichever is sooner. The statistical information will be calculated based upon ongoing blinded study data. Further details will be given in the Statistical Analysis Plan. With statistical information equivalent to 255 evaluable participants, the study will have greater than 90% power to detect a statistically significant (at overall 1 sided α = 0.025) dose-response relationship using a multiple comparison procedure-modelling (MCP-Mod) approach for the primary endpoint 'Change in the weekly average of daily NRS pain scores from baseline to Week 12'. This assumes that the true Week 12 placebo-corrected change from baseline difference at the CCI dose is 1.5, and the true dose-response follows a maximum response (Emax) relationship with a dose that produces half of the Emax (ED50) = CCI and a standard deviation (SD) = 2.4.	To increase the study sample size and ensure enough participants are recruited to achieve adequate study power.	Substantial

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
1.3 Schedule of Assessments (Table 1, footnote o)	On Day 1, ECG recording will be performed 30 to 60 minutes prior to IP administration (and prior to randomisation) and 4 hours ± 10 minutes after IP administration; 30 to 60 minutes prior to IP administration at Weeks 2, 4, 8, and 10; and thereafter at Week 12 and Week 32. ECG should be performed prior to any blood draw (Section 8.2.4).	On Day 1, ECG recording will be performed 30 to 120 ~~60~~ minutes prior to IP administration (and prior to randomisation) and 4 hours ± 30 ~~10~~ minutes after IP administration; 30 to 120 ~~60~~ minutes prior to IP administration at Weeks 2, 4, 8, and 10; and thereafter at Week 12 and Week 32. ECG should be performed prior to any blood draw (Section 8.2.4).	To offer more flexibility for procedures at the site without affecting the integrity of the data.	Non-substantial
4.1 Overall Design	This is a placebo-controlled Phase IIb study in which approximately 300 eligible participants will be randomly assigned to the IPs (one of 4 dose levels of MEDI7352 or placebo) to ensure that approximately 255 participants complete the treatment period.	This is a placebo-controlled Phase IIb study in which approximately 350 ~~300~~ eligible participants will be randomly assigned to the IPs (one of 4 dose levels of MEDI7352 or placebo) ~~to ensure that approximately 255 participants complete the treatment period~~.	To increase the study sample size.	Substantial
4.1.2 Additional Risk-Mitigation Procedures Implemented in the Context of the SARS-CoV-2/COVID-19 Pandemic	The following criteria should be met at baseline (prior to the first IP administration) and prior to all subsequent dosing visits: . . . . ∀ Study participants must have a body temperature < 37.8°C and show no clinical signs and symptoms consistent with COVID-19 infection or an acute viral respiratory illness. . . . . Participants with clinical signs and symptoms consistent with COVID-19 infection or an acute viral respiratory illness (eg, fever, cough, dyspnoea, sore throat, loss of taste/smell) or active COVID 19 infection confirmed by the appropriate laboratory test should not be considered eligible for IP administration. Also refer to exclusion criterion 30.	The following criteria should be met at baseline (prior to the first IP administration) and prior to all subsequent dosing visits: . . . . ∀ Study participants must have a body temperature < 37.8°C and show no clinical signs and symptoms consistent with COVID-19 infection ~~or an acute viral respiratory illness~~. . . . . Participants with clinical signs and symptoms consistent with COVID-19 infection ~~or an acute viral respiratory illness~~ (eg, fever, cough, dyspnoea, sore throat, loss of taste/smell) or active COVID-19 infection confirmed by the appropriate laboratory test should not be considered eligible for IP administration. Also refer to exclusion criterion 31 ~~30~~.	To expand eligibility while continuing to minimise the risk posed by SARS-CoV-2 to research participants, local investigational researchers, and other staff.	Substantial
4.1.2 Additional Risk-Mitigation	If a study participant is diagnosed with SARS-CoV-2 active infection and/or COVID 19 disease,	If a study participant is diagnosed with SARS-CoV-2 active infection and/or COVID 19 disease, IP	To resume IP administration in some	Substantial

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
Procedures Implemented in the Context of the SARS-CoV-2/COVID-19 Pandemic	IP administration should be permanently discontinued, and treatment should be provided according to the local area guidance; local-area quarantine guidance should also be followed (Refer to Section 7.1.1 and Section 7.1.2 for criteria for discontinuation of IP and procedures for discontinuation of IP, respectively).	administration should be ~~permanently discontinued~~ interrupted and treatment should be provided according to the local area guidance; local-area quarantine guidance should also be followed. To assess if the participant meets permanent IP discontinuation criteria, refer to Sections 7.1.1, ~~and Section~~ 7.1.2, and 7.1.3 for criteria for discontinuation of IP and procedures for temporary and permanent discontinuation of IP~~, respectively~~).	cases of resolved asymptomatic/mild COVID-19 infection.	
5.2 Exclusion Criteria (no 31)	Note that: • Any history of severe COVID-19 infection (eg, requiring hospitalisation, intensive care unit care, or assisted ventilation) or any prior COVID-19 infection with unresolved sequelae is exclusionary. Any acute SARS-COV-2/COVID-19 infection, including asymptomatic, mild, or moderate (lab confirmed or suspected based on clinical symptoms) within the last 3 months prior to screening or between screening and randomisation is exclusionary.	Note that: • Any history of severe COVID-19 infection (eg, requiring hospitalisation, intensive care unit care, or assisted ventilation) or any prior COVID-19 infection with unresolved sequelae is exclusionary. Any acute ~~SARS-COV-2/~~COVID-19 infection, including asymptomatic, mild, or moderate (lab confirmed or suspected based on clinical symptoms) ~~within the last 3 months~~ that is not resolved 1 month prior to ~~screening or between screening and~~ randomisation is exclusionary. [Note: a subject who has had an asymptomatic COVID-19 infection or recovered fully from a previous mild or moderate COVID-19 infection, without medical sequelae (including relevant negative testing that suggests they are no longer carrying replicating SARS-COV-2 virus), and remains well for at least 1 month prior to randomisation may be considered for study eligibility].	To expand eligibility while continuing to minimise the risk posed by SARS-CoV-2 to research participants, local investigational researchers, and other staff.	Substantial
6.5.2 Prohibited Concomitant Medications	The following treatments are prohibited during the study: • The use of analgesics other than rescue medication (paracetamol) including but not limited to opioids, topical applications of capsaicin, and formulations containing local	The following treatments are prohibited during the study: • The use of analgesics other than paracetamol rescue medication ~~(paracetamol)~~ (including but not limited to opioids, topical applications of capsaicin, and formulations containing local	Clarification to exclude potential ambiguity in the interpretation of the prohibited concomitant medications from the start of the washout period until	Non-substantial

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
	anaesthetic for OA pain treatment is prohibited from the start of the washout period until the Week 18 FU visit.	anaesthetic for OA pain treatment) is prohibited from the start of the washout period until the Week 18 FU visit.	the Week 18 FU visit. Non-substantial.	
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product	For any individual participant, further administration of IP will be stopped if any of the following scenarios occur: Reports of drug-related SAE(s) or drug-related AE (s) including but not necessarily limited to: • Serious or severe drug-related injection site reactions • Anaphylactic reaction, defined as an immediately life-threatening allergic reaction with bronchoconstriction, angioedema, and/or hypotension (FDA 2014); or serious hypersensitivity reactions • Development of moderate-to-severe sensory abnormalities (eg, paraesthesia, dysesthesia, burning, pins and needles) that are not resolved within a 14 day period • Development of peripheral neuropathy • New onset of demyelinating disorder • Serious systemic infection • Serious non-systemic infection if deemed necessary by the investigator	For any individual participant, further administration of IP will be stopped if any of the following scenarios occur: • Reports of drug-related SAE(s) or drug-related AE (s) including but not necessarily limited to: ! Serious or severe drug-related injection site reactions ! Anaphylactic reaction, defined as an immediately life-threatening allergic reaction with bronchoconstriction, angioedema, and/or hypotension (FDA 2014); or serious hypersensitivity reactions ! Development of moderate-to-severe sensory abnormalities (eg, paraesthesia, dysesthesia, burning, pins and needles) that are not resolved within a 14 day period ! Development of peripheral neuropathy ! New onset of demyelinating disorder ! Serious systemic infection ! Serious non-systemic infection if deemed necessary by the investigator	Bullet formatting corrected in this section.	Non-substantial
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product	For any individual participant, further administration of IP will be stopped if any of the following scenarios occur: . . . . • A positive test for SARS-CoV-2 at any time point	For any individual participant, further administration of IP will be stopped if any of the following scenarios occur: . . . . ~~• A positive test for SARS-CoV-2 at any time point~~	As COVID-19 continues to occur in a wide-spread manner at the population level and participants with a recent mild or asymptomatic infection do not represent a population	Substantial

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
	• Symptoms or signs consistent with COVID-19 infection or an acute viral illness (eg, fever, cough, dyspnoea), confirmed by the appropriate laboratory test	• ~~Symptoms or signs consistent with COVID-19 infection or an acute viral illness (eg, fever, cough, dyspnoea), confirmed by the appropriate laboratory test~~ • Development of COVID-19 infection that meets moderate or severe severity AE criteria. • Treatment with anti-SARS-CoV-2 monoclonal antibodies for COVID-19 infection of any severity. • Mild or asymptomatic COVID-19 infection with symptoms that have not resolved within 28 days since the last IP administration or results of appropriate testing for COVID-19 infection (ie, antigen-based) suggesting that a participant is carrying a replicating virus and remains positive within 28 days since the last IP administration. • There are other ongoing sequelae from COVID-19 infection, or the participant requires treatment for the manifestations of COVID-19 infection for the period beyond 28 days since the previous IP administration, or less than 5 half-lives have passed since the last COVID-19 antiviral medications administration within the 28 day period since the last IP administration	at high risk for inadequate antibody responses when treated with TNF inhibition, it is reasonable to allow participants with recent mild (or asymptomatic) COVID-19 infection to continue dosing, provided that 1) they have demonstrated negative testing (ie antigen-based) that suggests they are no longer carrying replicating virus, 2) symptoms have resolved and no ongoing treatments are required, 3) there are no other ongoing sequelae from infection, 4) and no more than 28 days have elapsed since the previous IP administration	
7.1.3 Temporary Discontinuation of Investigational Product	Withholding IP administration temporarily may be considered in the following cases	Withholding IP administration temporarily may be considered in the following cases . . . . • A positive test for SARS-CoV-2 at any time point during participation in the study. • Symptoms or signs consistent with COVID-19 infection (eg, fever, cough, dyspnoea), confirmed by an appropriate laboratory test.	To add certain COVID-19 scenarios to the temporary discontinuation of IP criteria and to describe to outline the conditions when IP administration could be resumed in case of resolved asymptomatic or mild COVID-19 infection.	Substantial

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
		Administration of IP can be resumed if deemed appropriate by the investigator in participants with fully resolved asymptomatic or mild COVID-19 infection (confirmed by negative SARS-CoV-2 testing (ie, antigen-based), that suggests that the participant is no longer carrying replicating virus) provided that it is completely resolved without sequalae within 28 days since the previous IP administration and participants do not require ongoing treatment for COVID-19 infection as well as do not have ongoing adverse drug reactions associated with treatment of COVID-19 infection as assessed by the investigator. Additionally, more than 5 half-lives of COVID-19 antiviral medications should elapse before IP administration is resumed. Participants who were treated with anti-SARS-CoV-2 monoclonal antibodies are not eligible for further IP administration. For participants treated with COVID-19 antiviral medications, the investigator should contact the medical monitor and agree if and when further IP administration is appropriate.		
8 Study Assessments (Double-blind Treatment Period)	The following procedures will be performed on Day 1 prior to randomisation: . . . . • ECG (30 to 60 minutes prior to IP administration and prior to any blood draw) . . . . The following procedures will be performed on Day 1 after randomisation and administration of IP: • ECG will be performed 4 hours ± 10 minutes after IP administration.	The following procedures will be performed on Day 1 prior to randomisation: . . . . • ECG (30 to ~~60~~ 120 minutes prior to IP administration and prior to any blood draw) . . . . The following procedures will be performed on Day 1 after randomisation and administration of IP: • ECG will be performed 4 hours ± ~~10~~ 30 minutes after IP administration.	To offer more flexibility for procedures at the site without affecting the integrity of the data.	Non-substantial
8.2.4 Electrocardiograms	On Day 1, ECG recording will be performed 30 to 60 minutes prior to IP administration (and prior to randomisation) and 4 hours ± 10 minutes after IP administration. On all other dosing days, ECG recording will be performed at 30 to 60 minutes	On Day 1, ECG recording will be performed 30 to 120 ~~60~~ minutes prior to IP administration (and prior to randomisation) and 4 hours ± 30 ~~10~~ minutes after IP administration. On all other dosing days, ECG recording will be performed at 30 to 120 ~~60~~ minutes	To offer more flexibility for procedures at the site without affecting the integrity of the data.	Non-substantial

Section and Name	Text in CSP version 3.0	Amended or New Wording in CSP version 4.0, Amendment 3 (Deletions struckthrough, additions underlined)	Brief Rationale	Substantial/ non-substantial
	prior to IP administration; thereafter, ECGs will be recorded at Week 12 and Week 32. ECG recording should be performed prior to any blood draw.	prior to IP administration; thereafter, ECGs will be recorded at Week 12 and Week 32. ECG recording should be performed prior to any blood draw.		
9.2 Sample Size Determination	Approximately 300 eligible participants will be randomly assigned to double-blind treatment with one of 4 dose levels of MEDI7352 or placebo to ensure that approximately 255 participants complete the treatment period. With 255 evaluable participants, the study will have greater than 90% power to detect a statistically significant (at overall 1-sided α = 0.025) dose-response relationship using a MCP-Mod approach for each of the primary endpoint 'Change in the weekly average of daily NRS pain scores from baseline to Week 12'. This assumes that the true Week 12 placebo-corrected change from baseline difference at the CCI dose is 1.5, the true dose-response follows a maximum response (E_{max}) relationship with a dose that produces half of the E_{max} (ED_{50}) = CCI and a SD = 2.4.	Approximately 350~~300~~ eligible participants will be randomly assigned to IPs (MEDI7352 or placebo) ~~to ensure that approximately 255 participants complete the treatment period~~. Recruitment will continue until the planned power of the study is achieved (ie, when statistical information equivalent to 255 participants completing the treatment period is reached) or approximately 350 randomised patients, whichever is sooner. The statistical information will be calculated based upon ongoing blinded study data. Further details will be given in the Statistical Analysis Plan. With statistical information equivalent to 255 evaluable participants, the study will have greater than 90% power to detect a statistically significant (at overall 1-sided α = 0.025) dose-response relationship using a MCP-Mod approach for ~~each of~~ the primary endpoint: Change in the weekly average of daily NRS pain scores from baseline to Week 12. This assumes that the true Week 12 placebo-corrected change from baseline difference at the CCI dose is 1.5, and the true dose-response follows a maximum response (E_{max}) relationship with a dose that produces half of the E_{max} (ED_{50}) = CCI and a SD = 2.4.	To increase the study sample size and ensure enough participants are recruited to achieve adequate study power.	Substantial

Abbreviations are found in Appendix L.

Amendment 2 (14 October 2021)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The Protocol Amendment Summary of Changes Table for the Amendment 2 is presented on the following pages.

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Overall Design)	The study consists of a screening period of up to 45 days, a 12-week treatment period, and a 20-week follow up (FU) period (Table 1).	The study consists of a screening period of up to 45 days, a 12-week treatment period, and a 24 ~~20~~-week follow up (FU) period (Table 1).	To follow participants for longer after the last IP administration to monitor joint-related AEs.	Substantial
1.1 Synopsis (Overall Design)	After the end-of-treatment (EOT) visit at Week 12, participants will enter the FU period, which comprises 3 clinic visits (Weeks 18, 28, and 32) and 3 FU phone calls (Weeks 15, 21, and 24).	After the end-of-treatment (EOT) visit at Week 12, participants will enter the FU period, which comprises 3 clinic visits (Weeks 18, ~~28, and~~ 32, and 36) and ~~3~~ 4 FU phone calls (Weeks 15, 21, ~~and~~ 24, and 28).	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.1 Synopsis (Interim Analysis) 4.1 Overall Design 9.5 Interim Analyses	The study incorporates 2 interim analyses: (1) a futility analysis will take place when approximately 25% of participants are evaluable for the primary endpoint; this analysis will assess the likely success of the study outcome and will enable the sponsor to make a go/no go decision regarding continuation of the study; and (2) an administrative analysis of efficacy data will take place when approximately 50% of participants are evaluable for the primary endpoint; this analysis will enable the sponsor to plan future project-related activities, but without making any changes to the current study.	The study incorporates 2 interim analyses: (1) a futility analysis will take place when approximately 25% of participants are evaluable for the primary endpoint; this analysis will assess the likely success of the study outcome and will enable the sponsor to make a go/no go decision regarding continuation of the study; and (2) an interim ~~administrative~~ analysis of efficacy data will take place when approximately 50% of participants are evaluable for the primary endpoint; this analysis will enable the sponsor to plan future project-related activities, but without making any changes to the current study.	Clarification that both analyses are interim	Non-substantial
1.1 Synopsis (Intervention Groups and Duration)	FU period: 20 week FU period with a final FU visit at Week 32 (± 7 days) The maximum study duration for each participant is approximately 44 weeks. The overall study duration is expected to be 24 months (12 months of active screening and enrolment, 10 months of treatment and FU, and 2 months for database lock).	FU period: 24 ~~20~~ week FU period with a final FU visit at Week 36 ~~32~~ (± 7 days) The maximum study duration for each participant is approximately 50 ~~44~~ weeks. The overall study duration is expected to be 31 ~~24~~ months (18 ~~12~~ months of active screening and enrolment, 11 ~~10~~ months of treatment and FU, and 2 months for database lock).	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Data Monitoring Committees) 9.6 Data Monitoring Committee	• Independent Efficacy Review Committee: This committee will independently review, interpret, and make decisions on future conduct of the clinical study based on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes.	• Independent Efficacy Review Group ~~Committee~~: This group ~~committee~~ will be independent~~ly~~ of the study team and will review, interpret, and make decisions on future conduct of the clinical study based on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes.	To reflect the change in Appendix B5.	Non-substantial
1.2 Schema	Figure: Follow-up (20 weeks) Phone calls: Weeks 15, 21, 24 Weeks: ….32	Figure: Follow-up (24 ~~20~~ weeks) Phone calls: Weeks 15, 21, 24, 28 Weeks:…32, 36	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	Follow-up period [b] (20 weeks)	Follow-up period [b] (24 ~~20~~ weeks)	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	W 21 & 24 D 147 & 168 Phone calls 2 & 3	W 21, ~~&~~ 24, & 28 D 147, ~~&~~ 168, & 196 Phone calls 2, & 3, & 4	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	W 28 ± 7 d D 196	W 32 ~~28~~ ± 7 d D 224 ~~196~~	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	W 32 ± 7 d D 224	W 36 ~~32~~ ± 7 d D 252 ~~224~~	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	CCI [redacted]			Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
1.3 Schedule of assessments	CCI			Non-substantial
1.3 Schedule of assessments	Footnote b: For participants who discontinued IP early, the 3 FU clinic visits and 3 phone calls will occur at the times indicated below (Section 7.1.2): ! … ! FU visit 2: Corresponds to Week 28; to be performed 18 weeks after the last IP administration ! FU visit 3: Corresponds to Week 32; to be performed 22 weeks after the last IP administration ! FU phone calls 1, 2, and 3: Corresponds to Weeks 15, 21, and 24, respectively; to be conducted 5, 11, and 14 weeks after the last IP administration, respectively	Footnote b: For participants who discontinued IP early, the 3 FU clinic visits and 4 ~~3~~ phone calls will occur at the times indicated below (Section 7.1.2): ! … ! FU visit 2: Corresponds to Week 32 ~~28~~; to be performed 22 ~~18~~ weeks after the last IP administration ! FU visit 3: Corresponds to Week 36 ~~32~~; to be performed 26 ~~22~~ weeks after the last IP administration ! FU phone calls 1, 2, ~~and~~ 3, and 4: Corresponds to Weeks 15, 21, ~~and~~ 24, and 28, respectively; to be conducted 5, 11, ~~and~~ 14, and 18 weeks after the last IP administration, respectively	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	Footnote h: If other major joints (elbows, wrists, and ankles) exhibit signs or symptoms associated with OA, these should also be imaged during screening. At the Week 28 follow up visit, safety X-ray imaging will be performed on knee and hip joints only.	Footnote h: If other major joints (elbows, wrists, and ankles) exhibit signs or symptoms associated with OA, these should also be imaged during screening. At the Week 32 ~~28~~ follow up visit, safety X-ray imaging will be performed on knee and hip joints only.	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	o On Day 1, ECG recording will be performed 30 to 60 minutes prior to IP administration (and prior to randomisation) and 4	o On Day 1, ECG recording will be performed 30 to 60 minutes prior to IP administration (and prior to randomisation) and 4 hours ± 10 minutes	Time points of visits updated due to change	Substantial (consequential)

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	hours ± 10 minutes after IP administration; 30 to 60 minutes prior to IP administration at Weeks 2, 4, 8, and 10; and thereafter at Week 12 and Week 28.	after IP administration; 30 to 60 minutes prior to IP administration at Weeks 2, 4, 8, and 10; and thereafter at Week 12 and Week 32 ~~28~~.	in the duration of the FU period	
1.3 Schedule of assessments	CCI			Non-substantial
1.3 Schedule of assessments	s On Day 1, injection site reactions will be monitored at 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after IP administration.	s On Day 1, injection site reactions will be monitored at approximately 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after completion of IP administration.	Clarification to allow for the practicalities of assessment taking into consideration 2 IP injections	Non-substantial
1.3 Schedule of assessments	t A urine pregnancy test (applicable for women who are not surgically sterile) should be performed and the results assessed at all dosing visits prior to IP administration and at the Week 32 visit.	t A urine pregnancy test (applicable for women who are not surgically sterile) should be performed and the results assessed at all dosing visits prior to IP administration and at the Week 36 ~~32~~ visit.	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
1.3 Schedule of assessments	CCI			Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	CCI			
1.3 Schedule of assessments				Non-substantial
2.2 Background	One of the most common causes of chronic pain and disability is OA, which is a slowly progressive joint disease affecting cartilage and subchondral bone.	One of the most common causes of chronic pain and disability is OA, which is a ~~slowly~~ progressive whole joint disease involving structural alterations in the hyaline articular cartilage, ~~affecting cartilage and~~ subchondral bone, ligaments, capsule, synovium, and periarticular muscles. The complex pathogenesis of OA involves mechanical, inflammatory, and metabolic factors, which ultimately lead to structural destruction and failure of the synovial joint.	More recent OA definition.	Non-substantial
2.2.2 Clinical Experience with MEDI7352	As of 18 July 2020, 2 clinical studies with MEDI7352 are ongoing: • The Phase I study D5680C00001 is a placebo-controlled, interleaved single-ascending dose (SAD) and multiple-ascending dose (MAD) clinical study in participants with pain associated with OA of the knee. The study is assessing the overall safety and tolerability of MEDI7352, as well as PK, immunogenicity (presence of antidrug antibodies [ADA]), and PD. • The Phase II study D5680C00002 is a randomised, double-blind, placebo-controlled, dose-response study to evaluate the efficacy and safety of MEDI7352 in participants with painful diabetic neuropathy (PDN). Although the study data remain blinded, it is estimated—based on the study randomisation	As of 01 June 2021 ~~18 July 2020~~, one clinical study of MEDI7352 has been completed ~~2 clinical studies with MEDI7352 are ongoing~~: • The Phase I study D5680C00001 was ~~is~~ a placebo-controlled, interleaved single-ascending dose (SAD) and multiple-ascending dose (MAD) clinical study in participants with pain associated with OA of the knee. The study assessed ~~is assessing~~ the overall safety and tolerability of MEDI7352, as well as PK, immunogenicity (presence of antidrug antibodies [ADA]), and PD. In the SAD phase, the MEDI7352 IV doses studied were 0.3, 2, 10, 50, 250, and 1000 µg/kg; the CCI dose was 50 µg/kg. In the MAD phase, participants received repeated IV doses (4 total) of MEDI7352 (1, 5, 50, 150, or 450 µg/kg) administered every 2 weeks. Two clinical studies with MEDI7352 are ongoing:	Status of MEDI7352 studies updated	Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	schemes—that approximately 107 of 157 participants have been exposed to MEDI7352 (single or multiple doses) in the Phase I (D5680C00001) and Phase II (D5680C00002) studies as of 23 April 2020 (the data cut-off date). **Phase I Study D5680C00001 (Participants with Painful Osteoarthritis of the Knee)** As of 23 April 2020, the SAD phase of the study (Cohorts 1 through 7) has been completed. The first 4 cohorts of the MAD phase (Cohorts 8 through 11) have also been completed; the fifth and final cohort (Cohort 12) was ongoing as of 23 April 2020. In all, 33 participants have received single IV doses of MEDI7352 ranging from 0.3 to 1000 µg/kg, and 6 participants have received single [C] doses of MEDI7352 50 µg/kg. In the ongoing MAD phase, an estimated 51 participants have received repeated IV doses of MEDI7352 ranging from 1 to 450 µg/kg every 2 weeks (Q2W) (up to 4 planned doses). No clinically relevant safety or tolerability concerns have been raised during the dose escalation in the SAD phase or in the MAD cohorts evaluated to date. A review of blinded safety data shows that 81 of 124 treated participants have had at least one reported treatment-emergent adverse event (TEAE). There have been no deaths during the study. No serious TEAEs or investigational product (IP) discontinuations due to TEAEs were reported during the SAD phase of the study.	• The Phase II study D5680C00002 is a randomised, double-blind, placebo-controlled, dose-response study to evaluate the efficacy and safety of MEDI7352 in participants with painful diabetic neuropathy (PDN). Participants will receive up to 6 planned IV doses administered every 2 weeks. • The Phase I study D5680C00004 is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and immunogenicity of MEDI7352 in healthy Japanese and Caucasian volunteers. Participants will receive up to 4 planned [C] injections every 2 weeks. ~~Although the study data remain blinded, it is estimated—based on the study randomisation schemes—that approximately 107 of 157 participants have been exposed to MEDI7352 (single or multiple doses) in the Phase I (D5680C00001) and Phase II (D5680C00002) studies as of 23 April 2020 (the data cut-off date).~~ **Phase I Study D5680C00001 (Participants with Painful Osteoarthritis of the Knee)** ~~As of 23 April 2020, the SAD phase of the study (Cohorts 1 through 7) has been completed. The first 4 cohorts of the MAD phase (Cohorts 8 through 11) have also been completed; the fifth and final cohort (Cohort 12) was ongoing as of 23 April 2020. In all, 33 participants have received single IV doses of MEDI7352 ranging from 0.3 to 1000 µg/kg, and 6 participants have received single [C] doses of MEDI7352 50 µg/kg. In the ongoing MAD phase, an estimated 51 participants have received repeated IV~~		

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	During the ongoing MAD phase of the study, there has been one reported serious TEAE (pneumonia), which led to the participant's withdrawal from the study. The pneumonia event 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). In addition, 4 participants were withdrawn from the MAD phase of the study due to non-serious TEAEs: viral upper respiratory infection (one participant), erysipelas left leg (one participant), fever and common cold (one participant), and infusion-related reaction, ie, dyspnoea, flushing, dizziness (one participant). The viral upper respiratory infection was considered not related to IP by the investigator; all other TEAEs were considered related to IP by the investigator. In the SAD phase of the study, the most commonly reported TEAEs (≥ 5% of participants) were headache (9 of 53 participants) and back pain (3 of 53 participants). In the MAD phase of the study, the most commonly reported TEAEs (≥ 5% of participants) were nasopharyngitis (20 of 71 participants), headache (18 of 71 participants), back pain (8 of 71 participants), oropharyngeal pain (6 of 71 participants), and nausea, pain in extremity, cough, and rhinorrhoea (4 of 71 participants each).	~~doses of MEDI7352 ranging from 1 to 450 µg/kg every 2 weeks (Q2W) (up to 4 planned doses).~~ No clinically relevant safety or tolerability concerns were ~~have been~~ raised during the dose escalation in the SAD ~~phase~~ or ~~in the~~ MAD phases of the study ~~cohorts evaluated to date~~. In the SAD phase, 17 of 39 participants (43.6%) treated with MEDI7352 (across all dose levels) and 9 of 14 participants (64.3%) treated with placebo had at least one treatment emergent adverse event (TEAE). Most TEAEs were considered by the investigator to be of 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 participants 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 participants treated with placebo, the most common TEAEs were headache (28.6%) and oropharyngeal pain (14.3%). In the MAD phase, 44 of 53 participants (83.0%) treated with MEDI7352 (across all dose levels) and 16 of 22 participants (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 participant treated with MEDI7352), which led to the participant'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).		

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	Most TEAEs were considered by the investigator to be of mild intensity. Four participants had TEAEs that were considered by the investigator to be of severe intensity: one participant with a non-serious TEAE of influenza, one participant with a non-serious TEAE of abdominal pain, one participant with non-serious TEAEs of pain in right knee and back pain, and one participant with a serious TEAE of pneumonia. The event of pneumonia led to the participant's withdrawal from the study, as described above. All TEAEs were considered not related to IP by the investigator. No clinically significant changes or dose-related trends have been observed for any other safety parameters in either study phase, including laboratory safety tests, vital signs, electrocardiogram (ECG) assessments, physical examinations, or neuropathy assessments (Total Neuropathy Score-nurse [TNSn]). There have been no reports of rapidly progressive OA (RPOA) or osteonecrosis. **Phase II Study D5680C00002 (Participants with Painful Diabetic Neuropathy)** The Phase II study D5680C00002 comprises 3 successive stages, each assessing MEDI7352 (up to 6 planned IV doses per participant) versus placebo as follows: Stage 1 assessed MEDI7352 5 µg/kg or placebo, Stage 2 is assessing MEDI7352 150 µg/kg or placebo, and Stage 3 will assess MEDI7352 10, 50, 150, and 450 µg/kg or placebo. At the time of preparation of this clinical study protocol (CSP), Stage 1 of the study is complete, and Stage 2 is ongoing. A	Four participants 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 participants treated with MEDI7352 had TEAEs of oral herpes and urinary tract infection (5.7% each) compared with participants treated with placebo (0%). However, the overall incidence of TEAEs in the SOC of infections and infestations was similar among participants treated with MEDI7352 and those treated with placebo (39.6% and 36.4%, respectively). The most common TEAEs among participants 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 participants 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 participant 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 participants with and without ADA in either study phase, suggesting that there were no apparent effects of immunogenicity on safety.		

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	total of 33 participants with PDN have received blinded IP (up to 6 planned IV doses, administered Q2W). It is estimated that 17 participants have received MEDI7352 (5 µg/kg or 150 µg/kg) and 16 participants have received placebo. A review of blinded safety data shows that 20 of 33 treated participants have had at least one reported TEAE as of 23 April 2020. There have been no deaths or serious TEAEs. One participant in Stage 1 discontinued after 5 of 6 planned infusions of IP due to a non-serious TEAE of cellulitis that was considered by the investigator to be of moderate intensity and not related to IP. The following TEAEs have been reported for ≥ 3 of treated participants overall: headache (6 participants) and nasopharyngitis (4 participants). Headache was the most commonly reported TEAE in each stage: 3 of 10 participants (30.0%) in Stage 1 (5 µg/kg MEDI7352 or placebo) and 3 of 23 participants (13.0%) in Stage 2 (150 µg/kg MEDI7352 or placebo). Most TEAEs reported in each study stage were considered by the investigator to be of mild intensity, and none were considered to be severe. 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 TNSn or for parameters measured during motor and sensory nerve conduction studies.	No clinically significant changes or dose-related trends for mean changes from baseline or differences between MEDI7352- and placebo-treated participants 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). ~~A review of blinded safety data shows that 81 of 124 treated participants have had at least one reported treatment-emergent adverse event (TEAE). There have been no deaths during the study. No serious TEAEs or investigational product (IP) discontinuations due to TEAEs were reported during the SAD phase of the study.~~ ~~During the ongoing MAD phase of the study, there has been one reported serious TEAE (pneumonia), which led to the participant's withdrawal from the study. The pneumonia event 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).~~ ~~In addition, 4 participants were withdrawn from the MAD phase of the study due to non-serious TEAEs: viral upper respiratory infection (one participant), erysipelas left leg (one participant), fever and common cold (one participant), and infusion-related reaction, ie, dyspnoea, flushing, dizziness (one participant). The viral upper respiratory infection was considered not related to IP by the investigator; all~~		

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	A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI7352 is provided in the current IB.	~~other TEAEs were considered related to IP by the investigator.~~ ~~In the SAD phase of the study, the most commonly reported TEAEs (≥ 5% of participants) were headache (9 of 53 participants) and back pain (3 of 53 participants).~~ ~~In the MAD phase of the study, the most commonly reported TEAEs (≥ 5% of participants) were nasopharyngitis (20 of 71 participants), headache (18 of 71 participants), back pain (8 of 71 participants), oropharyngeal pain (6 of 71 participants), and nausea, pain in extremity, cough, and rhinorrhoea (4 of 71 participants each).~~ ~~Most TEAEs were considered by the investigator to be of mild intensity. Four participants had TEAEs that were considered by the investigator to be of severe intensity: one participant with a non-serious TEAE of influenza, one participant with a non-serious TEAE of abdominal pain, one participant with non-serious TEAEs of pain in right knee and back pain, and one participant with a serious TEAE of pneumonia. The event of pneumonia led to the participant's withdrawal from the study, as described above. All TEAEs were considered not related to IP by the investigator.~~ ~~No clinically significant changes or dose-related trends have been observed for any other safety parameters in either study phase, including laboratory safety tests, vital signs, electrocardiogram (ECG) assessments, physical examinations, or neuropathy assessments (Total Neuropathy Score-nurse [TNSn]). There have been no reports of rapidly progressive OA (RPOA) or osteonecrosis.~~		

		Phase II Study D5680C00002 (Participants with Painful Diabetic Neuropathy) The Phase II study D5680C00002 comprises 4 ~~3~~ successive stages, each assessing MEDI7352 (up to 6 planned IV doses per participant) versus placebo as follows: Stage 1 assessed MEDI7352 5 µg/kg or placebo, Stage 2 assessed ~~is assessing~~ MEDI7352 150 µg/kg or placebo, Stage 3 will assess MEDI7352 450 µg/kg or placebo, and Stage 4 ~~3~~ will assess MEDI7352 10, 50, 150, and 450 µg/kg or placebo. At the time of preparation of this clinical study protocol (CSP), Stages ~~Stage~~ 1 and 2 of the study are ~~is~~ complete, and Stage 3 ~~2~~ is ongoing. ~~A total of 33 participants with PDN have received blinded IP (up to 6 planned IV doses, administered Q2W). It is estimated that 17 participants have received MEDI7352 (5 µg/kg or 150 µg/kg) and 16 participants have received placebo.~~ A review of blinded safety data showed ~~shows~~ that 26 ~~20~~ of 41 ~~33~~ treated participants (63.4%) have had at least one reported TEAE as of 01 June 2021 ~~23 April 2020~~. There have been no deaths or serious TEAEs. Three participants 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, 5 µg/kg MEDI7352 or placebo) • A TEAE of infection (symptoms of sore throat, fever, nasopharyngitis, tongue burning, and sweating) of mild intensity (Stage 2, 150 µg/kg 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 participant's		

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		withdrawal after 3 of 6 planned infusions of IP (150 µg/kg MEDI7352 or placebo). Headache was the most commonly reported TEAE overall: 7 of 41 participants (17.1%), including 3 of 10 participants (30.0%) in the completed Stage 1 (5 µg/kg MEDI7352 or placebo), 3 of 26 participants (11.5%) in the completed Stage 2 (150 µg/kg MEDI7352 or placebo) and 1 of 5 participants (20%) in the ongoing Stage 3 (MEDI7352 450 µg/kg or placebo). All TEAEs reported in each study stage were considered by the investigator to be of mild or moderate intensity. ~~One participant in Stage 1 discontinued after 5 of 6 planned infusions of IP due to a non-serious TEAE of cellulitis that was considered by the investigator to be of moderate intensity and not related to IP.~~ ~~The following TEAEs have been reported for ≥ 3 of treated participants overall: headache (6 participants) and nasopharyngitis (4 participants).~~ ~~Headache was the most commonly reported TEAE in each stage: 3 of 10 participants (30.0%) in Stage 1 (5 µg/kg MEDI7352 or placebo) and 3 of 23 participants (13.0%) in Stage 2 (150 µg/kg MEDI7352 or placebo).~~ ~~Most TEAEs reported in each study stage were considered by the investigator to be of mild intensity, and none were considered to be severe.~~ 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 TNSn or for parameters measured during motor and sensory nerve conduction studies.		

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		Phase I Study D5680C00004 (Healthy Japanese and Caucasian Volunteers) Two of the of 5 treated participants (40.0%) have had a total of 4 TEAEs as follows (one participant each): dyspepsia, catheter site erythema, injection site pain, and paraesthesia. All reported AEs were considered by the investigator to be of mild intensity. There have been no deaths, treatment-emergent SAEs, or withdrawals due to AEs. A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI7352 is provided in the current IB.		
2.3.1.1 Potential Risks Based on Mechanisms of Action	The safety profile of MEDI7352 may include adverse reactions that are related to the expected pharmacological mechanisms of action, and thus may be comparable to those previously reported for both anti-NGF monoclonal antibodies undergoing development (eg, tanezumab, fulranumab, and fasinumab) and established anti-TNFα therapies (eg, etanercept).	The safety profile of MEDI7352 may include adverse reactions that are related to the expected pharmacological mechanisms of action, and thus may be comparable to those previously reported for both anti-NGF monoclonal antibodies undergoing development (eg, tanezumab, fulranumab, and fasinumab) and established anti-TNFα therapies (eg, etanercept, adalimumab, and infliximab).	Updated to align with most recent version of the IB	Non-substantial
2.3.1.1 Potential Risks Based on Mechanisms of Action	Rapidly Progressive Osteoarthritis and other Joint Safety Events A dose-related increase in the incidence of RPOA was confirmed in later studies of tanezumab in participants with moderate-to-severe OA (Berenbaum et al 2019, Schnitzer et al 2019). Emerging Phase III data are consistent with joint safety events occurring more frequently with tanezumab than with placebo (Berenbaum et al 2019) or with NSAIDs (Hochberg et al 2019). Data from a Phase IIb/III study of fasinumab revealed a dose- and time-related increase in arthropathies, with a reported	Rapidly Progressive Osteoarthritis and other Joint Safety Events 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, SIF, and pathological fracture (FDA 2021a). There was a significantly higher incidence of events in participants treated with tanezumab (3.2% and 6.2% of participants treated with tanezumab 2.5 mg and 5 mg, respectively) compared to NSAIDs (1.5% of participants) or placebo (0% of participants) (FDA 2021c). In	Updated to align with most recent version of the IB	Non-substantial

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	5% incidence of RPOA in the fasinumab group (with joint space narrowing [RPOA 1] in 14 participants and with bony changes [RPOA-2] in 2 participants) compared to none in the placebo group. Subchondral insufficiency fracture occurred in 1.8% of participants in the combined fasinumab group and 1.2% in the placebo group. Most arthropathies (16 of 25) were discovered by a scheduled radiologic assessment (Dakin et al 2019). Given the dose-relatedness of anti-NGF to the incidence of RPOA, including destructive changes in the joints, it is thought that the risk of those events is likely related to the level of NGF sequestration. Additional information about this potential risk is provided in the current IB.	addition, a greater proportion of participants treated with tanezumab (5.5% and 7.8% of participants treated with tanezumab 2.5 mg and 5 mg, respectively) required total joint replacements when compared to those treated with NSAIDs (2.6% of participants) or placebo (4.5% of participants) (FDA 2021a, FDA 2021c). Overall, approximately 85% of the total joint replacements occurred in joints KL grade ≥ 3 at baseline (FDA 2021c); however, some joint safety events including total joint replacement occurred in joints KL grade 0 or 1 at baseline (FDA 2021a, FDA 2021c). It was also notable in the tanezumab programme that composite joint safety events are not limited to arthritis joints. For participants 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%) (FDA 2021b). ~~A dose-related increase in the incidence of RPOA was confirmed in later studies of tanezumab in participants with moderate-to-severe OA (Berenbaum et al 2019, Schnitzer et al 2019). Emerging Phase III data are consistent with joint safety events occurring more frequently with tanezumab than with placebo (Berenbaum et al 2019) or with NSAIDs (Hochberg et al 2019). Data from a Phase IIb/III study of fasinumab revealed a dose- and time-related increase in arthropathies, with a reported 5% incidence of RPOA in the fasinumab group (with joint space narrowing [RPOA 1] in 14 participants and with bony changes [RPOA-2] in 2 participants) compared to none in the placebo group. Subchondral insufficiency fracture occurred in 1.8% of participants in the combined~~		

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		~~fasinumab group and 1.2% in the placebo group. Most arthropathies (16 of 25) were discovered by a scheduled radiologic assessment (Dakin et al 2019). Given the dose-relatedness of anti-NGF to the incidence of RPOA, including destructive changes in the joints, it is thought that the risk of those events is likely related to the level of NGF sequestration.~~ ~~Additional information about this potential risk is provided in the current IB.~~		
2.3.1.1 Potential Risks Based on Mechanisms of Action	Autonomic Neuropathy and Sympathetic Dysfunction In the pooled analysis of safety data across tanezumab Phase III clinical studies (Tive et al 2019), AEs of postganglionic sympathetic dysfunction (AEs of decreased sympathetic function such as bradycardia, orthostatic hypotension, nausea, diarrhoea, or vomiting), occurred at similar rates in participants receiving placebo (4.3%), tanezumab (4.8%), or tanezumab plus NSAID (5.2%) in the overall population.	Autonomic Neuropathy and Sympathetic Dysfunction According to the FDA Briefing Document for the 2021 Advisory Committee meeting for tanezumab (FDA 2021a), in the Phase III placebo-controlled studies with tanezumab, AEs of postganglionic sympathetic dysfunction (AEs of decreased sympathetic function such as bradycardia, orthostatic hypotension, hypohidrosis, syncope), occurred at observation-time adjusted rates of 20.3%, 29.1%, and 46.2% for subjects receiving placebo, tanezumab 2.5 mg, and tanezumab 5.0 mg, respectively; the imbalance was primarily driven by higher rates of bradycardia and orthostatic hypotension in the tanezumab treatment groups. In a Phase III active-controlled study, AEs of postganglionic sympathetic dysfunction occurred at observation-time adjusted rates of 37.0%, 25.7%, and 36.1% for subjects receiving NSAIDs, tanezumab 2.5 mg, and tanezumab 5.0 mg, respectively. Overall, the FDA concluded that tanezumab was not found to be associated with an increased risk of sympathetic disfunction. ~~In the pooled analysis of safety data across tanezumab Phase III clinical studies (Tive et al 2019), AEs of postganglionic sympathetic dysfunction (AEs of decreased sympathetic function such as bradycardia,~~	Updated to align with most recent version of the IB.	Non-substantial

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		~~orthostatic hypotension, nausea, diarrhoea, or vomiting), occurred at similar rates in participants receiving placebo (4.3%), tanezumab (4.8%), or tanezumab plus NSAID (5.2%) in the overall population.~~		
2.3.1.1 Potential Risks Based on Mechanisms of Action	Additional warnings and precautions for etanercept include hypersensitivity reactions, exacerbation or new onset of demyelinating disease, malignancies, serious haematological reactions, new onset or worsening congestive heart failure, reactivation of hepatitis B, autoimmune hepatitis, autoimmune renal disease, and a lupus-like syndrome.	Patients older than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients with underlying conditions that may predispose to infection, such as advanced or poorly controlled diabetes. Additional warnings and precautions for etanercept 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.	Updated to align with most recent version of the IB.	Non-substantial
2.3.1.4 General Risk-Mitigation Plan	• Implementation of appropriate inclusion/exclusion criteria, baseline evaluations, and restrictions applied during the conduct of the clinical studies, specifically: # … # Exclusion of study participants with a history of RPOA, osteonecrosis, subchondral insufficiency fracture (SIF), avascular necrosis, and other significant arthropathies	• Implementation of appropriate inclusion/exclusion criteria, baseline evaluations, and restrictions applied during the conduct of the clinical studies, specifically: # … # Exclusion of study participants with a history of RPOA, osteonecrosis, ~~subchondral insufficiency fracture~~ (SIF~~)~~, avascular necrosis, and other significant arthropathies # Exclusion of study participants with preexisting clinically significant ~~sensory or~~ motor neuropathy	The risk-mitigation strategy is amended in line with the reassessment of important potential risks of the IP and to make the eligibility criteria more relevant for the population with common comorbidities who are representative of an OA population requiring chronic pain relief	Substantial

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	# Exclusion of study participants with preexisting clinically significant sensory or motor neuropathy # … # Exclusion of participants with a history of any malignancy, active liver disease, and psoriasis • Clinical safety monitoring and assessment procedures conducted at appropriate intervals at specified clinic visits during the clinical study, specifically including: # … # Follow-up (FU) required for cases of suspected neuropathy by neurologist and on protocol-prespecified cases of bradycardia, orthostatic hypotension, syncope, anhidrosis, or hypohidrosis by a neurologist and/or cardiologist (Section 8.2.2)	# … # ~~Exclusion of participants with a history of any malignancy, active liver disease, and psoriasis~~ • Clinical safety monitoring and assessment procedures conducted at appropriate intervals at specified clinic visits during the clinical study, specifically including: # … # Follow-up (FU) required for cases of suspected occurrence or worsening of neuropathy by neurologist and on protocol-prespecified cases of bradycardia, orthostatic hypotension, syncope, anhidrosis, or hypohidrosis by a neurologist and/or cardiologist (Section 8.2.2)		
2.3.2 Benefit Assessment	It is hypothesised that this analgesia at relatively low levels of NGF suppression results from synergistic engagement of NGF and TNF targets (see the current IB for maximum and average percentage of free NGF suppression following single IV doses of MEDI7352 in the Phase I study D5680C00001) . It may also be hypothesised that higher doses of MEDI7352 will be associated with increased TNFα suppression and could provide additional efficacy when compared to anti-NGF treatment alone.	It is hypothesised that this analgesia at relatively low levels of NGF suppression results from synergistic engagement of NGF and TNF targets ~~(see the current IB for maximum and average percentage of free NGF suppression following single IV doses of MEDI7352 in the Phase I study D5680C00001) . It may also be hypothesised that higher doses of MEDI7352 will be associated with increased TNFα suppression and could provide additional efficacy when compared to anti-NGF treatment alone~~.	Updated to align with most recent version of the IB	Non-substantial

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2.3.2 Benefit Assessment	Participants with painful OA of the knee, rather than healthy participants are being evaluated in the first-time-in-human (FTIH) SAD/MAD study with MEDI7352 (D5680C00001). The study remains blinded so no efficacy data are available at this stage. This Phase IIb study with MEDI7352 (D5680C00003) is being performed to characterise the dose-response relationship of MEDI7352 on pain in participants with chronic painful OA of the knee and to further assess MEDI7352 for safety, tolerability, PD, immunogenicity (ie, ADAs), and PK in this population.	The completed ~~Participants with painful OA of the knee, rather than healthy participants are being evaluated in the~~ first-time-in-human (FTIH) SAD/MAD study with MEDI7352 (D5680C00001) was conducted in participants with OA, rather than healthy participants, as there was the potential to observe at least some short-term efficacy signals in this population at some of the doses being administered. CCI [redacted] ~~The study remains blinded so no efficacy data are available at this stage.~~ MEDI7352 has been administered mainly to Caucasian participants to date. The ongoing study with MEDI7352 (D5680C00004) is being performed in healthy Japanese and Caucasian participants to allow a comparison of the safety, tolerability, PK and immunogenicity of MEDI7352 in both populations to support the participation of Japanese participants in ongoing and future clinical studies on MEDI7352 administered by the C CI route. This Phase IIb study with MEDI7352 (D5680C00003) is being performed to characterise the dose-response relationship of MEDI7352 on pain in participants with chronic painful OA of the knee and to further assess MEDI7352 for safety, tolerability, PK ~~PD~~, and immunogenicity (ie, ADAs)~~,~~ ~~and PK~~ in this population.	Updated to align with most recent version of the IB	Non-substantial
2.3.3 Overall Benefit/Risk Summary	The clinical data available to date from single-dose and multiple-dose IV administration of MEDI7352 to participants with painful OA of the knee have shown that most AEs were mild or	The clinical data available to date from single-dose and multiple-dose ~~IV~~ administration of MEDI7352 to participants with painful OA of the knee have shown that most AEs were mild or moderate in intensity and	Updated to align with most recent version of the IB	Non-substantial

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	moderate in intensity and unrelated to IP. There have been no clinically significant changes or trends for changes from baseline in safety parameters, including safety laboratory tests, vital signs, ECG assessments, physical examinations, or assessments of peripheral neurology. There have been no reports of destructive arthropathy. To date, a relatively small number of participants have been exposed to MEDI7352 across the ongoing Phase I and Phase II studies, so a full evaluation of risk/benefit is limited at present. Overall, no clinically important safety issues have emerged that preclude further evaluation of MEDI7352 in the relevant clinical study populations at repeated IV doses up to 450 µg/kg, and the benefit-risk evaluation remains favourable.	unrelated to IP. There have been no clinically significant changes or trends for changes from baseline in safety parameters, including safety laboratory tests, vital signs, ECG assessments, physical examinations, or assessments of peripheral neurology. There have been no reports of RPOA or destructive arthropathy. To date, a relatively small number of participants have been exposed to MEDI7352 across the ongoing Phase I and Phase II studies, so a full evaluation of risk/benefit is limited at present. ~~Overall, no clinically important safety issues have emerged that preclude further evaluation of MEDI7352 in the relevant clinical study populations at repeated IV doses up to 450 µg/kg, and the benefit-risk evaluation remains favourable.~~		
2.3.4 Overall Benefit/Risk Conclusion	Based on available information regarding the risks of MEDI7352 and the precautions included in the clinical studies for participants with OA, the risks are considered acceptable in relation to the potential long-term analgesic benefits for patients with painful OA.	Based on available information regarding the risks of MEDI7352 and the precautions included in the clinical studies to protect ~~for~~ participants with OA, the risks are considered acceptable in relation to the potential long-term analgesic benefits for patients with painful OA. Overall, no clinically important safety issues have emerged that preclude further evaluation of MEDI7352 in the relevant clinical study populations at exposures equivalent to those achieved with repeated IV doses up to 450 µg/kg. The MEDI7352 doses used in this study are supported by adequate safety margins, and the benefit-risk evaluation remains favourable for clinical development.	Updated to align with most recent version of the IB	Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
3 OBJECTIVES AND ENDPOINTS	CCI			Non-substantial (consequential)
3 OBJECTIVES AND ENDPOINTS	CCI			Non-substantial
4.1 Overall Design	The study consists of a screening period of up to 45 days (one or more visits), a 12 week double-blind treatment period (10 scheduled visits), and a 20-week FU period (3 scheduled visits and 3 phone calls).	The study consists of a screening period of up to 45 days (one or more visits), a 12 week double-blind treatment period (10 scheduled visits), and a 24 ~~20~~-week FU period (3 scheduled visits and 4 ~~3~~ phone calls).	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
4.1 Overall Design	All participants (ie, those who complete the treatment period and those who discontinue IP early) are expected to complete the EOT/ET visit and the 20-week FU period. The 20-week FU period consists of 3 clinic visits (Weeks 18, 28, and 32) and 3 FU phone calls (Weeks 15, 21, and 24). Safety X-ray imaging will be performed on the knee and hip joints at the Week 28 visit. The last study visit will occur at Week 32 to follow up on any new and clinically significant X-ray findings from Week 28.	All participants (ie, those who complete the treatment period and those who discontinue IP early) are expected to complete the EOT/ET visit and the 24 ~~20~~-week FU period. The 24 ~~20~~-week FU period consists of 3 clinic visits (Weeks 18, 32 ~~28~~, and 36 ~~32~~) and 4 ~~3~~ FU phone calls (Weeks 15, 21, 24, and 28 ~~24~~). Safety X-ray imaging will be performed on the knee and hip joints at the Week 32 ~~28~~ visit. The last study visit will occur at Week 36 ~~32~~ to follow up on any new and clinically significant X-ray findings from the Week 32 ~~28~~ visit.	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
4.1 Overall Design	The maximum study duration for each participant is approximately 44 weeks. The overall study duration is expected to be 24 months (12 months of active screening and enrolment, 10 months of treatment and FU, and 2 months for database lock). The primary database lock is targeted to occur 2 months after the last participant has completed the Week 32 FU visit.	The maximum study duration for each participant is approximately 50 ~~44~~ weeks. The overall study duration is expected to be 31 ~~24~~ months (18 ~~12~~ months of active screening and enrolment, 11 ~~10~~ months of treatment and FU, and 2 months for database lock). The primary database lock is targeted to occur 2 months after the last participant has completed the Week 36 ~~32~~ FU visit.	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
4.3 Justification for Dose	The highest repeated dose of 450 µg/kg was initiated only after the Safety Review Committee had reviewed blinded safety data from the completed SAD phase of the study and the completed MAD cohorts (MEDI7352 doses up to 150 µg/kg). To date, no safety or tolerability concerns have been reported.	~~The highest repeated dose of 450 µg/kg was initiated only after the Safety Review Committee had reviewed blinded safety data from the completed SAD phase of the study and the completed MAD cohorts (MEDI7352 doses up to 150 µg/kg). To date, no safety or tolerability concerns have been reported.~~ Further details of this study are provided in the IB.	Text deleted as study is now completed	Non-substantial
4.3 Justification for Dose	The rat 26-week toxicity study provides safety margins of 3.3 fold (maximum observed concentration [C_{max}] based) and 9.4 fold (average observed concentration over the dosing interval [$C_{average}$] based) for a MEDI7352 C CCI , whereas the cynomolgus monkey 26-week toxicity study provides safety margins of 17 fold (C_{max} based) and 52 fold ($C_{average}$ based).	The rat 26-week toxicity study provides safety margins of 3.2 ~~3.3~~ fold (maximum observed concentration [C_{max}] based) and 9.6 ~~9.4~~ fold (average observed concentration over the dosing interval [$C_{average}$] based) for a MEDI7352 C CCI , whereas the cynomolgus monkey 26-week toxicity study provides safety margins of 17 fold (C_{max} based) and 53 ~~52~~ fold ($C_{average}$ based).	Updated to align with most recent version of the IB	Non-substantial
4.3 Justification for Dose	Additional information about dose justification is provided in the IB.	~~Additional information about dose justification is provided in the IB.~~	Updated to align with IB	Non-substantial
5.1 Inclusion Criteria	5 The participant must be willing and able to discontinue all analgesic therapy with NSAID or COX 2 inhibitors from the start of the washout period until the end of the FU period.	5 The participant must be willing and able to discontinue ~~all~~ analgesic therapy for OA with NSAID or COX 2 inhibitors from the start of the washout period until the end of the FU period.	Clarification on indication added based allowing limited use NSAIDs/COX-2 inhibitors for other than OA self-limiting	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
			conditions after the Week 18 visit.	
5.1 Inclusion Criteria	14 A mean pain intensity score ≥ 5 in the target knee as measured on an 11 point NRS (0 to 10) by completion of a daily diary for 7 days prior to Day 1 (ie, Day 7 to Day 1, inclusive). At least 5 of 7 daily scores need to be recorded by the participant to obtain a valid baseline value.	14 A mean pain intensity score ≥ 5 in the target knee as measured on an 11 point NRS (0 to 10) by completion of a daily diary for 7 days prior to Day 1 (ie, Day 7 to Day 1, inclusive). At least 5 of 7 daily scores need to be recorded by the participant ~~to obtain a valid baseline value~~.	The "At least 5 of 7 daily scores" criterion was specified as a confirmation of participant diary compliance. Therefore this phrase has been removed so as to align with the planned statistical analysis of this endpoint.	Non-substantial
5.2 Exclusion Criteria	2 Previously received any form of anti-NGF, anti-TNF, or other biological DMARDs (including but not limited to golimumab, certolizumab, infliximab, adalimumab, etanercept, rituximab, abatacept, tocilizumab, and tofacitinib) within 12 months prior to screening or received other immunosuppressants within 6 months prior to screening (with the exception of inhaled or topical corticosteroids; for exclusionary intra-articular corticosteroids use, refer to exclusion criterion 37).	2 Previously received any form of anti-NGF; received ~~,~~ anti-TNFs including but not limited to golimumab, certolizumab, infliximab, adalimumab, etanercept, or rituximab within 12 months prior to screening, or other biological DMARDs (including but not limited to ~~golimumab, certolizumab, infliximab, adalimumab, etanercept, rituximab,~~ abatacept, tocilizumab, and tofacitinib), or ~~within 12 months prior to screening or received~~ other immunosuppressants within 6 months prior to screening (with the exception of inhaled or topical corticosteroids; for exclusionary intra-articular corticosteroids use, refer to exclusion criterion 36 ~~37~~).	Previous use of biological DMARDs modified to ease this particular eligibility criterion as the change is not considered to pose a safety risk to study participants.	Substantial
5.2 Exclusion Criteria	10 Diagnosis of RA. Evaluation for diagnostic purposes should include serology for anti-citrullinated protein antibodies (ACPA) at screening~~, and ACPA levels should be normal (for reference lab)~~	10 Diagnosis of RA. Evaluation for diagnostic purposes should include serology for anti-citrullinated protein antibodies (ACPA) at screening	Exclusion can be deferred to the investigator's judgement if ACPA level in the particular case is exclusionary	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
5.2 Exclusion Criteria	12 Current diagnosis of a comorbid condition known to be associated with other forms of arthritis or joint pathology other than OA, including but not necessarily limited to immunological or autoimmune diseases (eg, RA, lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis); psoriasis; seronegative spondyloarthropathies; or other diseases involving the target joint (including endocrinopathies, metabolic joint diseases, joint infections, Paget's disease, or tumours)	12 Current diagnosis of a comorbid condition known to be associated with other forms of arthritis or joint pathology other than OA, including but not necessarily limited to immunological or autoimmune diseases (eg, RA, lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis); ~~psoriasis;~~ seronegative spondyloarthropathies; or other diseases involving the target joint (including endocrinopathies, metabolic joint diseases, joint infections, Paget's disease, or tumours)	Participants with psoriasis that is not associated with comorbid arthropathy, that could affect efficacy or safety assessment in the study population, can be included.	Substantial
5.2 Exclusion Criteria	13 The following conditions (including screening imaging results suggestive of these conditions as per central reader evaluation) should be excluded: RPOA, primary osteonecrosis (including spontaneous osteonecrosis of the knee), SIF, avascular necrosis, osteoporotic fractures, atrophic OA, hip dislocation, congenital hip dysplasia with degenerative joint disease, excessive malalignment of the knee (anatomical axis angle greater than 10 degrees), pathological fractures, stress fracture or reaction, vertical tear of the posterior meniscal root, or large or extensive subchondral cysts.	13 The following conditions (<u>based on</u> ~~including~~ screening imaging results ~~suggestive of these conditions~~ as per central reader evaluation) should be excluded: RPOA, primary osteonecrosis (including spontaneous osteonecrosis of the knee), SIF, avascular necrosis, osteoporotic fractures, ~~atrophic OA,~~ hip dislocation, ~~congenital hip dysplasia with degenerative joint disease, excessive malalignment of the knee (anatomical axis angle greater than 10 degrees),~~ pathological fractures, <u>or</u> stress fracture or reaction~~, vertical tear of the posterior meniscal root, or large or extensive subchondral cysts~~.	Given the relatively short dosing period in this study and that the excluded imaging findings are common in an OA population, it is considered reasonable to include a broader OA population to study risk factors of RPOA and MEDI7352 safety. The conditions being removed are not considered as identified risk factors of RPOA based on the available data from clinical development programmes for anti-NGFs.	Substantial
5.2 Exclusion Criteria	14 History of significant trauma (eg, intra-articular fracture) or surgery (excluding injection therapies and arthroscopy) to a knee, hip, or shoulder within the previous year. Refer	14 History of significant trauma (eg, intra-articular fracture) ~~or surgery (excluding injection therapies and arthroscopy)~~ to a knee, hip, or shoulder within <u>1</u> ~~the previous~~ year <u>prior to screening or</u>	Surgery is moved to the procedures-related exclusion criteria.	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	to exclusion criterion 34 for nondiagnostic arthroscopy.	between screening and randomisation~~. Refer to exclusion criterion 34 for nondiagnostic arthroscopy~~.	Added clarification that condition is still exclusionary if it occurs between screening and randomisation	
5.2 Exclusion Criteria	16 Presence of neuropathic pain, complex regional pain syndrome, or the following chronic primary pain syndromes (per the eleventh edition of the International Classification of Diseases): fibromyalgia or chronic widespread pain.	16 Presence of neuropathic pain (except for pain related to tunnel neuropathies in upper limbs), ~~complex regional pain syndrome,~~ or ~~the following~~ chronic primary pain syndromes (per the eleventh edition of the International Classification of Diseases): eg, fibromyalgia ~~or chronic widespread pain~~.	Exception for tunnel neuropathies in upper limbs added to align with the modified exclusion criterion 18.	Substantial
5.2 Exclusion Criteria	18 Presence of clinically significant neuropathy (eg, hereditary neuropathy, diabetic neuropathy, inflammatory neuropathy, nerve compression injury, carpal tunnel syndrome) or other clinically significant disorder associated with sensory abnormalities	18 Presence of clinically significant neuropathy (eg, hereditary ~~neuropathy~~, autonomic or ~~diabetic neuropathy,~~ inflammatory neuropathy~~, nerve compression injury, carpal tunnel syndrome) or other clinically significant disorder associated with sensory abnormalities~~ Note: entrapment/tunnel neuropathy affecting the upper limbs that is considered stable is not necessarily excluded; sensory neuropathy that is considered stable and non-progressive for at least 6 months is not necessarily excluded. Note: for non-exclusionary neuropathies, there is a requirement for participants to undergo a baseline evaluation by a neurologist and to have relevant nerve conduction studies conducted and documented at baseline.	Make the eligibility criteria more relevant for the older population with OA who require pain relief with comorbidities such as tunnel and sensory neuropathies	Substantial
5.2 Exclusion Criteria	19 Requires ~~walker or~~ wheelchair for mobility	19 Requires wheelchair for mobility	Participants using walkers will be allowed to take part in the study	Substantial
5.2 Exclusion Criteria	22 Significant or chronic lung disease, including severe or unstable chronic obstructive pulmonary disease, severe or unstable asthma,	22 Significant or chronic lung disease, including severe or unstable chronic obstructive pulmonary disease, severe or unstable asthma, current pneumonitis, or interstitial lung disease	To allow inclusion of participants with past history of pneumonitis	Substantial

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	current ~~or past history of~~ pneumonitis, or interstitial lung disease		or interstitial lung disease who have been cured and whose condition is not ongoing	
5.2 Exclusion Criteria	23 Diabetes complicated with retinopathy (by history), neuropathy (by history or physical examination), or nephropathy. Uncomplicated, stable diabetes that is well controlled and actively managed is not exclusionary.	23 Diabetes complicated with retinopathy ~~(by history), neuropathy (by history or physical examination),~~ or nephropathy. Uncomplicated, stable diabetes that is well controlled and actively managed is not exclusionary. Haemoglobin A1c levels above 8.5 are exclusionary.	Clarification of the exclusionary levels of HbA1C for participants with diabetes	Substantial
5.2 Exclusion Criteria	24 Known or suspected systemic infection, including HIV, HBV, HCV, or TB should be excluded. If QuantiFERON test is positive at screening, participants will be excluded from the study.	24 Known or suspected systemic infection, including HIV, HBV, HCV, or TB should be excluded. If QuantiFERON test is positive at screening, participants will be excluded from the study except for the cases when the QuantiFERON test remains positive after the successful treatment of TB as confirmed and documented by the relevant specialist.	Provision to include participants with a positive QuantiFERON test after successful treatment of active or latent TB, as it is possible that the QuantiFERON test remains positive after successful treatment.	Substantial
5.2 Exclusion Criteria	26 History or evidence of any significant autoimmune disease or demyelinating disorder, including multiple sclerosis, optic neuritis, transverse myelitis, peripheral demyelinating neuropathy; history or current diagnosis of epilepsy; current diagnosis of autonomic neuropathy; active liver disease; or history of any underlying condition that predisposes participant to infections (such as splenectomy or primary or secondary immunodeficiency syndrome)	26 History or evidence of ~~any significant autoimmune disease or~~ demyelinating disorder, including multiple sclerosis, optic neuritis, transverse myelitis, ~~peripheral demyelinating neuropathy;~~ history or current diagnosis of epilepsy~~; current diagnosis of autonomic neuropathy; active liver disease; or history of any underlying condition that predisposes participant to infections (such as splenectomy or primary or secondary immunodeficiency syndrome)~~	Exclusionary autoimmune diseases are captured in exclusion criterion 12; exclusionary neuropathies are captured in exclusion criterion 18, exclusionary predisposition to infection is captured in exclusion criterion 31 for consistency. Participants with	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
			autoimmune diseases other than those listed in exclusion criterion 12 might be enrolled at the investigator's discretion provided that other eligibility criteria are met.	
5.2 Exclusion Criteria	27 History of ~~severe allergy/~~hypersensitivity reactions or ongoing ~~allergy~~/hypersensitivity reactions, ~~including a history of hypersensitivity to immunisations or immunoglobulins and/or biological therapies (eg, etanercept)~~	27 History of anaphylactic/severe hypersensitivity reactions, history of hypersensitivity to immunisations or immunoglobulins and/or biological therapies (eg, etanercept) or ongoing hypersensitivity reactions	Clarification that not all severe allergic reactions in the medical history are exclusionary	Substantial
5.2 Exclusion Criteria	28 History of cancer or diagnosis of cancer between screening and randomisation	28 Lifetime history of haematopoietic malignancies, history of other cancers within 5 years prior to screening except for cervical carcinoma in situ, in situ colon cancer, or non-invasive malignant colon polyps treated by excision at least 2 years ago with no evidence of recurrence . ~~History of cancer or d~~ Diagnosis of any cancer between screening and randomisation	To make the eligibility criteria more relevant for the older population with OA with common comorbidities including medical history of successfully treated cancer. Clarified that diagnosis of any cancer between screening and randomization is exclusionary.	Substantial
5.2 Exclusion Criteria	29 Transient ischaemic attack or stroke in the last 12 months prior to screening	29 Transient ischaemic attack in the last 6 months prior to screening or stroke in the last 12 months prior to screening; transient ischaemic attack or stroke between screening and randomisation	Possibility to decrease the time elapsed from transient ischemic attack to 6 months is aligned with the evaluation of potential	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
			risks related to MEDI7352 exposure Additional text to clarify exclusion of participants who have a transient ischaemic attack or stroke during the period between screening and randomisation.	
5.2 Exclusion Criteria	30 History of substance use disorders (SUD) including alcohol or recreational drugs according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) within 2 years prior to screening (with the exception of tobacco SUD)	30 History of substance use disorders (SUD) including alcohol or recreational drugs according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) within 2 years prior to randomisation ~~screening~~ (with the exception of tobacco SUD)	Text added to clarify that SUD prior to randomisation is exclusionary (including the period between screening and randomisation).	Substantial
5.2 Exclusion Criteria	31 Current active infection, chronic or persistent systemic infection, or serious or severe localized or systemic infection within 3 months prior to screening or between screening and randomisation. Note that: - Any history of severe COVID-19 infection (eg, requiring hospitalisation, intensive care unit care, or assisted ventilation) or any prior COVID-19 infection with unresolved sequelae is exclusionary. Any acute SARS-COV-2/COVID-19 infection, including asymptomatic, mild, or moderate (lab confirmed or suspected based on clinical symptoms) within the last 6 months prior to screening is also exclusionary.	31 Current active infection, chronic or persistent systemic infection, or serious or severe localized or systemic infection within 3 months prior to screening or between screening and randomisation, or history of any underlying condition that predisposes participant to infections (such as splenectomy or primary or secondary immunodeficiency syndrome). Note that: - Any history of severe COVID-19 infection (eg, requiring hospitalisation, intensive care unit care, or assisted ventilation) or any prior COVID-19 infection with unresolved sequelae is exclusionary. Any acute SARS-COV-2/COVID-19 infection, including asymptomatic, mild, or moderate (lab confirmed or suspected based on clinical symptoms) within the last 3 ~~6~~ months prior to screening or between screening and randomisation is ~~also~~ exclusionary.	Moved from exclusion criterion 26. Evolving knowledge of COVID-19 infection as well as data about the safety profile of MEDI7352 allows for restriction of the exclusionary period for asymptomatic, mild, or moderate SARS-COV-2/COVID-19 infection to 3 months prior to screening or between	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
			screening and randomisation	
5.2 Exclusion Criteria	32 Current serious or unstable clinically important illness, including respiratory, cardiovascular, gastrointestinal, endocrinologic, immunologic, haematologic, or neurological or other major disease that is likely to deteriorate or affect the participant's safety or ability to complete the study, as judged by the investigator	32 Current serious or unstable clinically important illness, including respiratory, cardiovascular, gastrointestinal, endocrinologic, immunologic, haematologic, or neurological or other major disease that is likely to deteriorate or affect the participant's safety or ability to complete the study, as judged by the investigator. Note: current diagnosis of cirrhosis of the liver is exclusionary.	Additional text added to clarify the exclusion of participants with cirrhosis of the liver.	Substantial
5.2 Exclusion Criteria	New criterion added as exclusion criterion 33	33 Family history of long QT syndrome Subsequent exclusion criteria renumbered	Moved from ECG-related criterion 44	Non-substantial
5.2 Exclusion Criteria	34 Nondiagnostic arthroscopy performed on the target knee joint within 180 days prior to screening; diagnostic arthroscopy performed within 90 days prior to screening	35 ~~34~~ History of surgery to a knee, hip, or shoulder within 1 year prior to screening or between screening and randomisation except for arthroscopy. Note: Nondiagnostic arthroscopy performed on the target knee joint within 180 days prior to screening; or diagnostic arthroscopy performed on the target knee joint within 90 days prior to screening are exclusionary. Arthroscopy performed between screening and randomisation is exclusionary.	Moved from exclusion criterion 14 for consistency Additional text to clarify exclusion of participants who have surgery to the knee, hip, or shoulder during the period between screening and randomisation.	Substantial
5.2 Exclusion Criteria	37 Intra-articular platelet-rich plasma treatment on the target joint within 6 months prior to screening	37 Intra-articular platelet-rich plasma treatment on the target joint within 6 months prior to screening or between screening and randomisation.	Additional text to clarify exclusion of participants who received intra-articular platelet-rich plasma treatment on the target joint during the period between screening and randomisation.	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
5.2 Exclusion Criteria	Exclusion criterion 44 • A corrected QT interval by Fredericia (QTcF) interval measurement of > 470 milliseconds or family history of long QT syndrome	Exclusion criterion 45 ~~44~~ • Note that a corrected QT interval by Fredericia (QTcF) interval measurement of◦>◦470◦milliseconds ~~or family history of long QT syndrome~~ is exclusionary.	To clarify exclusion criterion. Family history text moved to medical history exclusion criterion.	Non-substantial
5.2 Exclusion Criteria	45 Participant with > 2 × upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) or > ULN total bilirubin (> 1.5 × ULN if known Gilbert's syndrome) ~~∀~~ If a participant has elevations in total bilirubin only that are > ULN and < 1.5 × ULN, fractionated bilirubin should be checked to identify possible undiagnosed Gilbert's syndrome (eg, direct bilirubin < 35%).	46 ~~45~~ Participant with > 2 × upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) or > 1.5 × ULN total bilirubin ~~(> 1.5 × ULN if known Gilbert's syndrome)~~ ∀ ~~If a participant has elevations in total bilirubin only that are > ULN and < 1.5 × ULN, fractionated bilirubin should be checked to identify possible undiagnosed Gilbert's syndrome (eg, direct bilirubin < 35%).~~	Participants with baseline total bilirubin levels ≤ 1.5 × ULN due to the reasons that are not contradictory with other exclusion criteria are good candidates for the study.	Substantial
5.2 Exclusion Criteria	46 Estimated creatinine clearance < 60 ml/min at screening	47 ~~46~~ Estimated creatinine clearance ≤ 50 ~~< 60~~ ml/min at screening	Less stringent creatinine clearance cut-off to assess MEDI7352 safety in the relevant OA population where creatinine clearance 50 to 60 ml/min is a common finding.	Substantial
5.2 Exclusion Criteria	50 Participant requires aspirin at doses greater than 100 mg/day for cardiovascular prophylaxis or requires treatment with vitamin K dependent anticoagulant (eg, warfarin, coumadin), or nonvitamin K dependent novel oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban).	51 ~~50~~ Participant requires aspirin at doses greater than 325 ~~100~~ mg/day for cardiovascular prophylaxis or requires treatment with vitamin K dependent anticoagulant (eg, warfarin~~, coumadin), or nonvitamin K dependent novel oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban~~).	To make the eligibility criteria more relevant for the broader OA population with common comorbidities and medications required for their treatment	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
6.5.1 Permitted Concomitant Therapy	The following treatments are permitted, with restrictions: … • Medications for the treatment of nonexcluded medical conditions (eg, depression, hypertension, and diabetes mellitus) are permitted, including antihypertensive, cholesterol-lowering, and antidiabetic medications; antidepressants; and sedative/hypnotics as judged clinically acceptable by the investigator and the medical monitor.	The following treatments are permitted, with restrictions: … • Medications for the treatment of nonexcluded medical conditions (eg, depression, hypertension, and diabetes mellitus) are permitted, including antihypertensive, cholesterol-lowering, and antidiabetic medications; antidepressants; and sedative/hypnotics as judged clinically acceptable by the investigator ~~and the medical monitor~~.	Consultation with the medical monitor about all medications for non-exclusionary conditions is not mandatory. The new text on conditions when consultation with medical monitor about concomitant medications is advisable is added to this section.	Non-substantial
6.5.1 Permitted Concomitant Therapy	The following treatments are permitted, with restrictions: … • Low-dose aspirin up to 100 mg/day is permitted for cerebrovascular or cardiovascular prophylaxis.	The following treatments are permitted, with restrictions: … • Low-dose aspirin up to 325 ~~100~~ mg/day is permitted for cerebrovascular or cardiovascular prophylaxis.	To permit aspirin at the doses that are commonly used for cerebrovascular or cardiovascular prophylaxis	Substantial
6.5.1 Permitted Concomitant Therapy	New text added under "The following treatments are permitted, with restrictions:"	The following treatments are permitted, with restrictions: • Limited (no more than 10 days per 8-week period) concomitant use of prescription or OTC NSAIDs may be allowed on an occasional basis for self-limiting conditions not related to osteoarthritis (eg, migraine attack), after the Week 18 FU visit. The study medical monitor should be contacted for approval prior to use whenever possible, and all doses and days of use will be recorded in the eCRF.	Provision for limited use of NSAIDs during the FU period (after Week 18) to treat potential comorbidities with NSAIDs/ COX-inhibitors.	Substantial
6.5.1 Permitted Concomitant Therapy	New text added	If a new medication has to be introduced or the dose of concomitant medication needs to be changed during the double-blind treatment period, consultation with the medical monitor is advisable.	Clarification when investigators are expected to discuss concomitant therapy with a medical monitor.	Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
6.5.1 Permitted Concomitant Therapy	However, intra-articular injections/interventions, NSAIDs, COX-2 inhibitors, and aspirin (in doses that exceed 100 mg/day) are prohibited until after the last FU visit (Visit 13).	However, intra-articular injections/interventions, NSAIDs, COX-2 inhibitors, and aspirin (in doses that exceed 325 ~~100~~ mg/day) are prohibited until after the last FU visit (Visit 14 ~~13~~).	To align with the updated allowed dose of aspirin, and updated visit schedule	Substantial (consequential)
6.5.2 Prohibited Concomitant Medications	The following treatments are prohibited during the study: • Vitamin K-dependent anticoagulants (eg, warfarin, coumadin) or nonvitamin K dependent novel oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban) • The use of NSAIDs, COX-2 inhibitors, or aspirin (> 100 mg/day) at any time from the start of the washout period until after the last FU visit (Week 32) is prohibited. This includes OTC pain medications and topical analgesics that contain an NSAID or COX 2 inhibitor. For participants who discontinue IP early, NSAIDs, COX-2 inhibitors, or aspirin use is described in Section 7.1.2. • Use of analgesics other than paracetamol (including but not limited to weak opioids and topical applications of capsaicin and formulations containing local anaesthetic (eg, lidocaine) is prohibited from the start of the washout period until the Week 18 FU visit. • Any other investigational drug or device, including other immunotherapeutics • Live viral or attenuated bacterial vaccines are disallowed from 28 days prior to the first IP dose, during IP administration, and for 2 months after the last IP administration. • Oral, IV, intramuscular, or any other parenteral steroids (Note that inhaled	The following treatments are prohibited during the study: • ~~Vitamin K-dependent anticoagulants (eg, warfarin, coumadin) or nonvitamin K-dependent novel oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban~~) • The use of analgesics other than rescue medication (paracetamol) including but not limited to opioids, topical applications of capsaicin, and formulations containing local anaesthetic for OA pain treatment is prohibited from the start of the washout period until the Week 18 FU visit. • The use of NSAIDs, COX-2 inhibitors for OA treatment, or use of aspirin (> 325 ~~100~~ mg/day) at any time from the start of the washout period until after the last FU visit (Week 36 ~~32~~) is prohibited. This includes OTC pain medications and topical analgesics that contain an NSAID or COX 2 inhibitor. For participants who discontinue IP early, NSAIDs, COX-2 inhibitors, or aspirin use is described in Section 7.1.2. • ~~Use of analgesics other than paracetamol (including but not limited to weak opioids and topical applications of capsaicin and formulations containing local anaesthetic (eg, lidocaine) is prohibited from the start of the washout period until the Week 18 FU visit.~~ • ~~Any other investigational drug or device, including other immunotherapeutics~~ • COVID-19 vaccines	Amended in line with exclusion criteria updates. Reordered for clarity (medication prohibited during all study periods vs medications prohibited during prespecified study periods). As pre-screening restrictions are covered in the exclusion criteria, only restrictions applicable for the study should be detailed here. Clarification by removing medications use before participation in the study that is covered in exclusion criterion 2.	Substantial (consequential)

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	steroids for well-controlled chronic obstructive pulmonary disease or asthma or topical steroids for eczema are permitted). (Also refer to exclusion criteria 2 and 3.) • Any drug of abuse including but not limited to amphetamine, barbiturate, cannabis, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene, with the following exceptions: ! Sedative/hypnotics used as described above ! Barbiturates as a constituent of antimigraine medication (eg, Fioricet) ! Short-term sedation and/or analgesia if needed to perform study procedure (eg, MRI). (Note: These should not be given within 48 hours prior to a study visit or during the collection of ePRO pain data from Day -7 to Day -1 [inclusive] for baseline NRS pain evaluation.) • Muscle relaxants, anticonvulsants, anti-Parkinsonian medications, or neuroleptic medications, unless used for nonexcluded conditions such restless leg syndrome, are prohibited. • Corticosteroid injection or intra-articular hyaluronic acid injection on the target knee within 12 weeks prior to screening, corticosteroid injection on a nontarget joint within 12 weeks prior to screening, or intra-articular hyaluronic acid injection on a nontarget joint within 6 weeks prior to screening are prohibited. These therapies	! If a study participant is being considered for enrolment into the study and also for COVID-19 vaccination, the participant must not be randomised until 30 days after the last dose of COVID-19 vaccine or 'booster dose' (whichever is required to consider vaccination complete in line with applicable guidance). Note that this is applicable only to COVID-19 vaccines, irrespective of their modality, which are currently approved by Health Authorities or otherwise approved under relevant regulations, eg, emergency use authorisation (FDA)/conditional marketing authorisation (European Medicines Agency)/temporary supply (Medicines and Healthcare Products Regulatory Agency). • Live viral or attenuated bacterial vaccines are disallowed from 28 days prior to the first IP dose, during IP administration, and for 2 months after the last IP administration. ~~• Oral, IV, intramuscular, or any other parenteral steroids (Note that inhaled steroids for well-controlled chronic obstructive pulmonary disease or asthma or topical steroids for eczema are permitted). (Also refer to exclusion criteria 2 and 3.)~~ ~~• Any drug of abuse including but not limited to amphetamine, barbiturate, cannabis, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene, with the following exceptions:~~ ~~! Sedative/hypnotics used as described above~~		

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	are also prohibited during the study. (Note: Intra-articular injections are not permitted during the study with the exception of cases of ET when this treatment option is deemed necessary by the investigator. In such cases, initiation of intra-articular corticosteroid injections should be deferred until **at least 8 weeks** after the last IP administration.) • The following therapies are prohibited from 12 months prior to screening and during the study: ! Etanercept and medications known to interact with etanercept, specifically anakinra, abatacept, and sulfasalazine ! Other DMARDs, including but not limited to golimumab, certolizumab, infliximab, adalimumab, rituximab, tocilizumab, and tofacitinib ! Any other form of anti-TNF or anti-NGF therapy ! Other immunosuppressants are prohibited from within 6 months prior to screening and during the study. The restrictions related to use of intra-articular corticosteroid injections are mentioned above. • COVID-19 vaccines ! If a study participant is being considered for enrolment into the study and also for COVID-19 vaccination, the participant must not be randomised until 30 days after the last dose of COVID-19 vaccine or 'booster dose' (whichever is required	~~! Barbiturates as a constituent of antimigraine medication (eg, Fioricet)~~ ~~! Short-term sedation and/or analgesia if needed to perform study procedure (eg, MRI). (Note: These should not be given within 48 hours prior to a study visit or during the collection of ePRO pain data from Day -7 to Day -1 [inclusive] for baseline NRS pain evaluation.)~~ ~~• Muscle relaxants, anticonvulsants, anti-Parkinsonian medications, or neuroleptic medications, unless used for nonexcluded conditions such restless leg syndrome, are prohibited.~~ • ~~Corticosteroid injection or intra-articular hyaluronic acid injection on the target knee within 12 weeks prior to screening, corticosteroid injection on a nontarget joint within 12 weeks prior to screening, or intra-articular hyaluronic acid injection on a nontarget joint within 6 weeks prior to screening are prohibited. These therapies are also prohibited during the study. (Note:~~ Intra-articular injections are not permitted during the study, including the screening period, with the exception of cases of ET when this treatment option is deemed necessary by the investigator. In such cases, initiation of intra-articular corticosteroid injections should be deferred until **at least 8 weeks** after the last IP administration.~~)~~ • The following therapies are prohibited ~~from 12 months prior to screening and~~ during the study starting from the screening period (please also refer to exclusion criteria 2, 5, 36, 51):		

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	to consider vaccination complete in line with applicable guidance). Note that this is applicable only to COVID-19 vaccines, irrespective of their modality, which are currently approved by Health Authorities or otherwise approved under relevant regulations, eg, emergency use authorisation (FDA)/conditional marketing authorisation (European Medicines Agency)/temporary supply (Medicines and Healthcare Products Regulatory Agency).	! Etanercept and medications known to interact with etanercept, specifically anakinra, abatacept, and sulfasalazine ! Other DMARDs, including but not limited to golimumab, certolizumab, infliximab, adalimumab, rituximab, tocilizumab, and tofacitinib ! Any other form of anti-TNF or anti-NGF therapy ! Other immunosuppressants ~~are prohibited from within 6 months prior to screening and during the study~~. The restrictions related to use of intra-articular corticosteroid injections are mentioned above. ! Vitamin K-dependent anticoagulants (eg, warfarin) ! Oral, IV, intramuscular, or any other parenteral steroids (Note that inhaled steroids for well-controlled chronic obstructive pulmonary disease or asthma or topical steroids for eczema are permitted). ! Any drug of abuse including but not limited to amphetamine, barbiturate, cannabis, cocaine, methadone, methaqualone, opiate, phencyclidine, or propoxyphene, with the following exceptions: - Sedative/hypnotics used as described above - Barbiturates as a constituent of antimigraine medication (eg, Fioricet)		

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
		- Short-term sedation and/or analgesia if needed to perform study procedure (eg, MRI). (Note: These should not be given within 48 hours prior to a study visit or during the collection of ePRO pain data from Day -7 to Day -1 [inclusive] for baseline NRS pain evaluation.) ! Muscle relaxants, anticonvulsants, anti-Parkinsonian medications, or neuroleptic medications, unless used for nonexcluded conditions, such as restless leg syndrome, are prohibited. ! Any other investigational drug or device, including other immunotherapeutics • ~~COVID-19 vaccines~~ ! ~~If a study participant is being considered for enrolment into the study and also for COVID-19 vaccination, the participant must not be randomised until 30 days after the last dose of COVID-19 vaccine or 'booster dose' (whichever is required to consider vaccination complete in line with applicable guidance). Note that this is applicable only to COVID-19 vaccines, irrespective of their modality, which are currently approved by Health Authorities or otherwise approved under relevant regulations, eg, emergency use authorisation (FDA)/conditional marketing authorisation (European Medicines Agency)/temporary supply (Medicines and Healthcare Products Regulatory Agency).~~		

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
6.5.3 Rescue Medication	Participants who develop unacceptable pain during any stage of the study (including during the washout period and the period between completion of washout and randomisation) will be permitted to initiate rescue analgesic therapy with paracetamol using a dosing regimen that is aligned with local standards of prescribing practice and as described in the patient information leaflet and approved by the investigator.	Participants who develop unacceptable pain during ~~any stage of~~ the study until the Week 18 visit or ET visit, whichever is earlier (including during the washout period and the period between completion of washout and randomisation) will be permitted to initiate rescue analgesic therapy with paracetamol using a dosing regimen that is aligned with local standards of prescribing practice and as described in the patient information leaflet and approved by the investigator.	Wording amended to correct an inconsistency and to align with the study design where participants may be given standard of care therapy after the Week 18 visit (for participants who have completed treatment) or the ET visit (for participants for whom IP administration has been discontinued earlier) so there is no need to use paracetamol as rescue medication after those visits.	Non-substantial
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product	For any individual participant, further administration of IP will be stopped if any of the following scenarios occur: • Reports of drug-related SAE(s) or drug-related AE(s) including but not necessarily limited to: … # Renal toxicity, defined as serum creatinine ≥ 1.5 × ULN	For any individual participant, further administration of IP will be stopped if any of the following scenarios occur: • Reports of drug-related SAE(s) or drug-related AE(s) including but not necessarily limited to: … # ~~Renal toxicity, defined as serum creatinine ≥ 1.5 × ULN~~	Criterion removed to address the changes in exclusion criteria	Substantial (consequential)
7.1.2 Procedures for Early Discontinuation of Investigational Product	However, initiation of NSAIDs, COX-2 inhibitors, and aspirin (in doses that exceed 100 mg/day) is prohibited until after 5 half-lives following the last IP administration (ie, approximately 3 weeks).	However, initiation of NSAIDs, COX-2 inhibitors, and aspirin (in doses that exceed 325 ~~100~~ mg/day) is prohibited until after 5 half-lives following the last IP administration (ie, approximately 3 weeks).	To align with the updated allowed dose of aspirin	Substantial (consequential)

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
7.1.2 Procedures for Early Discontinuation of Investigational Product	All participants prematurely discontinued from IP are expected to complete the ET visit and the 20 week FU period, which consists of 3 FU clinic visits and 3 phone calls at the times indicated below: … • FU visit 2: Week 28 assessments to be performed 18 weeks after the last IP administration • FU visit 3: Week 32 assessments to be performed 22 weeks after the last IP administration	All participants prematurely discontinued from IP are expected to complete the ET visit and the 24 ~~20~~-week FU period, which consists of 3 FU clinic visits and 4 ~~3~~ phone calls at the times indicated below: … • FU phone call 4 ~~visit 2~~: To be conducted ~~Week 28 assessments to be performed~~ 18 weeks after the last IP administration • FU visit 2 ~~3~~: Week 32 assessments to be performed 22 weeks after the last IP administration • FU visit 3: Week 36 assessments to be performed 26 weeks after the last IP administration	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
7.1.3 Temporary Discontinuation of Investigational Product	Withholding IP administration temporarily may be considered in the following cases: ... • AE suggestive of peripheral neuropathy	Withholding IP administration temporarily may be considered in the following cases: ... • AE suggestive of new occurrence or worsening of peripheral neuropathy	Updated criterion in line with updated exclusion criterion 18	Substantial (consequential)
7.1.3 Temporary Discontinuation of Investigational Product	Participants with AEs suggestive of peripheral neuropathy as per investigator's neurological assessment should be evaluated by a neurologist as soon as possible. … The participant should not be dosed with the subsequent dose of IP until (if applicable) the absence of sensory abnormalities, sympathetic dysfunction, peripheral neuropathy or Class 3 or Class 4 (NYHA 1994) heart failure have been confirmed, or RPOA, SIF, primary osteonecrosis, or pathological fracture have been excluded.	Participants with AEs suggestive of new occurrence or worsening of peripheral neuropathy as per investigator's neurological assessment should be evaluated by a neurologist as soon as possible. … The participant should not be dosed with the subsequent dose of IP until (if applicable) the absence of sensory abnormalities, sympathetic dysfunction, new occurrence or worsening of peripheral neuropathy or Class 3 or Class 4 (NYHA 1994) heart failure have been confirmed, or RPOA, SIF, primary osteonecrosis, or pathological fracture have been excluded.	Updated in line with updated exclusion criterion 18	Substantial (consequential)

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
7.3 Lost to Follow-up	The following actions must be taken if a participant fails to return to the clinic for a required study visit: … • Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to FU. The participant will be classified as lost to FU only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study (ie, Week 32) despite all the above listed efforts. For the primary analysis purposes, a participant will be classified as lost to FU if he/she has failed to return for the required study visits and his/her vital status remains unknown at the time of primary database lock (ie, after the Week 32 visit).	The following actions must be taken if a participant fails to return to the clinic for a required study visit: … • Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to FU. The participant will be classified as lost to FU only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study (ie, Week 36 ~~32~~) despite all the above listed efforts. For the primary analysis purposes, a participant will be classified as lost to FU if he/she has failed to return for the required study visits and his/her vital status remains unknown at the time of primary database lock (ie, after the Week 36 ~~32~~ visit).	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
8 STUDY ASSESSMENTS AND PROCEDURES (Study Periods and Visits)*	The study consists of a total of at least 13 clinic visits and 3 phone calls: one (or more) screening visit(s); 9 scheduled visits during the double-blind treatment period, 3 scheduled visits during the FU period, and 3 phone calls during the FU period.	The study consists of a total of at least 14 ~~13~~ ~~clinic~~ visits and 4 ~~3~~ phone calls: one (or more) screening visit(s); 10 ~~9~~ scheduled visits during the double-blind treatment period, 3 scheduled visits during the FU period, and 4 ~~3~~ phone calls during the FU period.	Number of visits updated due to change in the duration of the FU period	Substantial (consequential)
8 STUDY ASSESSMENTS AND PROCEDURES (Double-blind Treatment Period)	CCI [redacted]			Non-substantial
8 STUDY ASSESSMENTS AND PROCEDURES	• Blood for haematology/chemistry/ coagulation, PK, ADAs, ~~NGF,~~ CCI [redacted], CCI [redacted]	• Blood collection for haematology, chemistry, coagulation, PK, ADAs, PD, and CCI [redacted] CCI [redacted]	Minor edit in wording	Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
(Double-blind Treatment Period)				
8 STUDY ASSESSMENTS AND PROCEDURES (Double-blind Treatment Period)	Injection site reactions will be monitored at 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after IP administration.	Injection site reactions will be monitored at approximately 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after completion of IP administration.	Clarification to allow for the practicalities of assessment taking into consideration 2 IP injections	Non-substantial
CCI				Non-substantial
8 STUDY ASSESSMENTS AND PROCEDURES (Early Termination/ Follow-up Visit)	The 20-week FU period consists of 3 clinic visits (at Weeks 18, 28, and 32) and 3 phone calls (at Weeks 15, 21, and 24). Safety X-ray imaging will be performed on the knee and hip joints at the Week 28 visit. Any potentially clinically significant findings detected on the X ray assessment performed at the Week 28 visit will be further assessed and adjudicated (if needed) by the final FU visit at Week 32.	The 24 ~~20~~-week FU period consists of 3 clinic visits (at Weeks 18, 32 ~~28~~, and 36 ~~32~~) and 4 ~~3~~ phone calls (at Weeks 15, 21, 24, and 28 ~~24~~). Safety X-ray imaging will be performed on the knee and hip joints at the Week 32 ~~28~~ visit. Any potentially clinically significant findings detected on the X ray assessment performed at the Week 32 ~~28~~ visit will be further assessed and adjudicated (if needed) by the final FU visit at Week 36 ~~32~~.	Number and time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
8.2.2 Neurological Examinations	A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs: • An AE suggestive of peripheral neuropathy	A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs: • An AE suggestive of new occurrence or worsening of peripheral neuropathy	The language on FU of peripheral neuropathy during the study has been amended to align with the possibility of	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	• AE of abnormal sensation such as allodynia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, or sensory loss	• AE of new occurrence or worsening of abnormal sensation such as allodynia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, or sensory loss	inclusion of some non-exclusionary neuropathies	
8.2.2 Neurological Examinations	None: new text	For participants with clinical manifestations consistent with worsening of pre-existing neuropathy, follow-up nerve conduction studies should be performed and documented at the time points deemed appropriate by the neurologist, but at least once during participation in the study.	Guidance on FU of worsening of non-exclusionary neuropathy added.	Substantial
8.2.2 Neurological Examinations	The participant should not be dosed with the subsequent dose of IP until the absence of peripheral neuropathy or another neurological condition that meets prespecified criteria for IP discontinuation has been confirmed.	The participant should not be dosed with the subsequent dose of IP until the absence of the ~~peripheral neuropathy or another~~ neurological condition that meets prespecified criteria for IP discontinuation has been confirmed.	Language on the FU of peripheral neuropathy during the study has been amended to align with the possibility of inclusion of some non-exclusionary neuropathies	Substantial
8.2.4 Electrocardiograms	On all other dosing days, ECG recording will be performed at 30 to 60 minutes prior to IP administration; thereafter, ECGs will be recorded at Week 12 and Week 28.	On all other dosing days, ECG recording will be performed at 30 to 60 minutes prior to IP administration; thereafter, ECGs will be recorded at Week 12 and Week 32 ~~28~~.	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
8.2.6.1 Radiographic (X-ray) Assessment	At the Week 28 visit, safety X-ray imaging will be performed on the knee and hip joints. Any potentially clinically significant findings detected on X-ray performed at Week 28 will be further assessed and adjudicated (if needed) by the final FU visit (Week 32).	At the Week 32 ~~28~~ visit, safety X-ray imaging will be performed on the knee and hip joints. Any potentially clinically significant findings detected on X-ray performed at Week 32 ~~28~~ will be further assessed and adjudicated (if needed) by the final FU visit (Week 36 ~~32~~).	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
8.2.9 Injection Site Reactions	On Day 1, injection site reactions will be monitored at 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after IP administration.	On Day 1, injection site reactions will be monitored at approximately 5, 15, 30, 45, and 60 minutes and 2 and 4 hours after completion of IP administration.	Clarification to allow for the practicalities of assessment taking into	Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
			consideration 2 IP injections	
8.2.10 Procedures for Subjects Undergoing Joint Replacement	Participants who permanently discontinue IP will be asked to complete study assessments at the ET visit as soon as possible and then to enter the FU period.	It is recommended to have at least 3 weeks between IP administration and joint replacement surgery. Participants ~~who permanently discontinue IP~~ will be asked to complete study assessments at the ET visit as soon as possible and then to enter the FU period.	Recommendation on the minimum period between IP administration and joint replacement surgery added	Substantial
8.2.10 Procedures for Subjects Undergoing Joint Replacement	None: new text	Wherever possible, the surgeon's assessment of procedural difficulty (uneventful; minor complications (including but not limited to impaired wound healing); or major complications (taking into consideration the participant's medical history and physical condition prior to surgery) should be collected as well.	Additional information that is expected to be collected in joint replacement surgery cases added	Substantial
8.2.10 Procedures for Subjects Undergoing Joint Replacement	AEs that led to joint replacement surgery should be followed up by the investigator for as long as medically indicated but no less than up to the end of the FU period.	AEs that led to joint replacement surgery should be followed up by the investigator for as long as medically indicated but no less than up to the end of the FU period or 4 months since joint replacement surgery (whichever is longer). Data on additional or corrective procedures (for example a revision or implant replacement) that were necessary after total joint replacement and their outcomes should be collected wherever possible as well.	The minimal duration of FU period to assess joint replacement surgery outcomes and additional information that is expected to be collected in joint replacement surgery cases is added	Substantial
8.2.11.3 Urine Drug Screen	The urine drug test will be performed only at screening (Table 1).	The urine drug test will be performed at the time points shown in ~~only at screening (~~Table 1~~)~~.	To clarify time points in the text and correct discrepancy with Table 1	Non-substantial
8.3.5 Adverse Events of Special Interest	The following AESIs have been identified specifically for this MEDI7352 protocol and are to be reported as described in Section 8.3.1 through Section 8.3.4.	The following AESIs have been identified specifically for this MEDI7352 protocol and are to be reported as described in Section 8.3.1 through Section 8.3.4. • …	Additional events have been added to AESIs for safety data collection and monitoring purposes	Substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	• … • Anaphylactic reactions and injection site reactions that lead to discontinuation of administration of IP	• Anaphylactic reactions; serious or severe hypersensitivity reactions; or ~~and~~ injection site reactions that lead to permanent discontinuation of administration of IP		
CCI				Non-substantial
8.6.1.1 Pharmacodynamic Biomarkers	Results from the PD biomarker analyses will be ~~reported in~~ the CSR.	Results from the PD biomarker analyses may ~~will~~ be presented separately from the CSR.	For consistency with Section 9.4.4.2.	Non-substantial
CCI				Non-substantial
				Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
		CCI		
Appendix B 5	**Independent Efficacy Review Committee** The role of the Independent Efficacy Review Committee is to independently review, interpret and adjudicate on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes. The committee will make recommendations to the sponsor, based on these analyses, on the future conduct of the trial and in particular on whether to continue, terminate or modify the study. To do so, the committee will make their recommendations on the basis of access to unblinded data at both the participant and treatment group level. Along with a recommendation, the committee will provide sufficient contextual information such that the sponsor can determine whether and how to implement the recommendation. The Independent Efficacy Review Committee will consist of, at a minimum, the following members: rheumatologist, statistician, and pain specialist.	**Independent Efficacy Review Group ~~Committee~~** The role of the Independent Efficacy Review Group ~~Committee~~ is to independently review, interpret and adjudicate on the proposed interim analyses for futility and efficacy and on any additional analyses carried out for administrative purposes. The group ~~committee~~ will make recommendations to the study team ~~sponsor~~, based on these analyses, on the future conduct of the trial and in particular on whether to continue, terminate or modify the study. To do so, the group ~~committee~~ will make their recommendations on the basis of access to unblinded data at both the participant and treatment group level. Along with a recommendation, the group ~~committee~~ will provide sufficient contextual information such that the study team ~~sponsor~~ can determine whether and how to implement the recommendation. The Independent Efficacy Review Group ~~Committee~~ will consist of sponsor personnel who are independent of the study team. The ~~precise committee~~ membership, responsibilities, and procedures applicable to the Independent Efficacy	To clarify that the members of the Independent Efficacy Review Group are sponsor personnel who are independent of the study team	Non-substantial

Section # and Name	Initial Wording under Amendment 1	Amended or New Wording under Amendment 2 (Deletions are strikethrough, and additions are underlined)	Brief Rationale	Substantial/ Non-substantial
	The precise committee membership, responsibilities, and procedures applicable to the Independent Efficacy Review Committee will be detailed in its charter.	Review Group ~~Committee~~ will be detailed in its charter.		
Appendix I	Footnote a for Table I11: Scheduled X-ray at Week 28 is required for hips and knees only.	Footnote a for Table I11: Scheduled X-ray at Week 32 ~~28~~ is required for hips and knees only.	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)
Appendix I	Table I12: Knee: At screening and at Week 28 (or FU clinic Visit 2 for participants who discontinued IP early) and as clinically indicated during the study Hip: At screening and at Week 28 (or FU clinic Visit 2 for participants who discontinued IP early) and as clinically indicated during the study [a]	Table I12: Knee: At screening and at Week 32 ~~28~~ (or FU clinic Visit 2 for participants who discontinued IP early) and as clinically indicated during the study Hip: At screening and at Week 32 ~~28~~ (or FU clinic Visit 2 for participants who discontinued IP early) and as clinically indicated during the study [a]	Time points of visits updated due to change in the duration of the FU period	Substantial (consequential)

Abbreviations are found in Appendix L.

Amendment 1 (11 March 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This global amendment 1 supersedes all global or country-specific protocol addendums dated prior to the date of this amendment as it incorporates the requirements detailed in these addendums.

Overall Rationale for the Amendment:

This protocol (study D5680C00003) has been amended to outline the approaches to COVID-19 vaccination in the current clinical study protocol (CSP) in the context of the current pandemic of coronavirus respiratory disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); to correct and/or clarify inclusion/exclusion criteria, timing of assessments on Day 1, timing for rescreening subjects, rescreening procedures, and to revise, add, or remove minor text as needed to increase clarity or correct interpretation of the protocol.

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
1.2 Schema	The screening period is up to 45 days, and one rescreening attempt is allowed during this period.	The screening period is up to 45 days; ~~and~~ one rescreening attempt is allowed ~~during this period~~. (Section 5.4.1).	To provide one rescreening opportunity for study participants	Non-substantial
1.3 Schedule of assessments	None: new footnote added to column "Wk 0 (Day 1)"	[c] For additional information on timing of assessments to be performed on Day 1 (ie, before randomisation, prior to IP administration, and after IP administration), see Section 8 "Double-blind Treatment Period."	To indicate section of the CSP where timing of Day 1 assessments can be found	Non-substantial
1.3 Schedule of assessments	New footnote added to column headings V4 and V5	[f] On study Visit 4 (Day 14) and Visit 5 (Day 28), study participants will remain under observation for at least 2 hours after IP administration.	Added based on the recommendations made by the Danish Medicines Agency to provide longer onsite monitoring of potential acute reactions after the second and third CCI IP administration	Substantial
1.3 Schedule of assessments	[y] The screening will be implemented until there is no perceived risk from COVID-19 for participants to take part in the study; COVID-19 symptom screening, body temperature check, and RNA testing may also be conducted at other time points at the discretion of the investigator. [z] The RNA test will be implemented until there is no perceived risk from COVID-19 for participants to take part in the study; Sample to be taken no earlier than 72 hours prior to each dosing day (Days 1, 14, 28, 42, 56, and 70) (Section 4.1.2)..	[bb] The screening will be implemented until there is no perceived risk from COVID-19 for participants to take part in the study; COVID-19 symptom screening, body temperature check, and ~~RNA~~ SARS-CoV-2 testing may also be conducted at other time points at the discretion of the investigator. [cc] The ~~RNA~~ SARS-CoV-2 test will be implemented until there is no perceived risk from COVID-19 for participants to take part in the study; a test sample to be taken ~~no earlier~~ within 72 hours prior to each dosing ~~day~~ visit (on Days 1, 14, 28, 42, 56, and 70) (Section 4.1.2).	To clarify the definition and timing of COVID-19 testing before a visit	Non-substantial
3 Objectives and Endpoints	CCI [redacted]			Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	CCI			
4.1 Overall Design	One rescreening attempt is allowed during this period.	One rescreening attempt is allowed ~~during this period~~. (Section 5.4.1).	To provide one rescreening opportunity for study participants	Non-substantial
4.1.2 Additional Risk-Mitigation Procedures Implemented in the Context of the SARS-CoV-2/ COVID-19 Pandemic	• Study participants must be tested once for SARS-CoV-2 ribonucleic acid (RNA) at baseline (within 72 hours of randomisation) and prior to all dosing visits (within 72 hours of IP administrations). All tests must be negative before each IP dose is administered. Treatment options should be discussed with the participant if the COVID-19 test is positive.	• Study participants must be tested once for SARS-CoV-2 ~~ribonucleic acid (RNA)~~ at baseline (within 72 hours of randomisation) and prior to all dosing visits (within 72 hours of IP administrations). All tests must be negative before each IP dose is administered. The SARS-CoV-2 test should have sufficient sensitivity and specificity for detection of SARS-CoV-2 and should meet the accepted local or regional public health standards for screening of asymptomatic subjects. Treatment options should be discussed with the participant if the COVID-19 test is positive.	To provide more options for SARS-CoV-2 testing once new tests with acceptable standards would become available	Non-substantial
4.1.2 Additional Risk-Mitigation Procedures Implemented in the Context of the SARS-CoV-2/	• Where applicable, additional local requirements for the definition of a SARS-CoV2-RNA negative result should be satisfied. These may include but are not necessarily limited to the need for repeat testing for SARS-CoV2-RNA.	• Where applicable, additional local requirements for the definition of a SARS-CoV2~~-RNA~~ negative test result should be satisfied. These may include but are not necessarily limited to the need for ~~repeat~~ repeating ~~testing for~~ the SARS-CoV2~~-RNA~~ test.	To provide more options for SARS-CoV-2 testing once new tests with acceptable standards would become available	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
COVID-19 Pandemic				
4.1.2 Additional Risk-Mitigation Procedures Implemented in the Context of the SARS-CoV-2/ COVID-19 Pandemic	• No earlier than 72 hours prior to each dosing visit, COVID-19 nose swab and/or throat/saliva swab will be performed according to local laboratory standards and protocols for sample acquisition.	• ~~No earlier than~~ Within 72 hours-prior to each dosing visit, COVID-19 nose swab and/or throat/saliva swab will be performed according to local laboratory standards and protocols for sample acquisition.	To provide clarity on definition of SARS-CoV-2/COVID-19 testing 72 hours before a visit	Non-substantial
5.1 Inclusion Criteria (Diagnostic)	12 Participant has a documented history of inadequate pain relief from past or ongoing treatment with NSAIDs/COX-2 inhibitors, acetaminophen (paracetamol), and opioids (weak or strong). The participant is expected to have tried all specified analgesic classes either consecutively or simultaneously (including in combination products) within recommended dosing guidelines for at least 2 weeks unless contraindicated (see below). • Participants who have intolerability or contraindications to NSAIDs/COX-2 inhibitors must have documented history that acetaminophen (paracetamol) and opioid treatment, either consecutively or simultaneously (including in combination products) within recommended dosing guidelines for at least 2 weeks, at any time, has not provided sufficient pain relief. • Participants who have intolerability or contraindications to opioids must have documented history that acetaminophen (paracetamol) and NSAID/COX-2 inhibitors treatment, either consecutively or simultaneously (including in combination products) within recommended dosing	12 ~~Participant has a~~ Documented history of inadequate pain relief from past or ongoing treatment according to the recommended dosing guidelines with acetaminophen (paracetamol) **and** oral NSAIDs/COX-2 inhibitors unless contraindicated/not tolerated **and** opioids unless (a) opioids are contraindicated/not tolerated, (b) there is no access to opioids as per local standards of care, or (c) the patient is unwilling to take opioids. (Note that ongoing strong opioids are exclusionary.) ~~with NSAIDs/COX-2 inhibitors, acetaminophen (paracetamol), and opioids (weak or strong). The participant is expected to have tried all specified analgesic classes either consecutively or simultaneously (including in combination products) within recommended dosing guidelines for at least 2 weeks unless contraindicated (see below).~~ • ~~Participants who have intolerability or contraindications to NSAIDs/COX-2 inhibitors must have documented history that acetaminophen (paracetamol) and opioid treatment, either consecutively or simultaneously (including in combination products) within recommended dosing guidelines for at least 2 weeks, at any time, has not provided sufficient pain relief.~~	To provide opportunity for inclusion of difficult-to-treat patients who are unwilling to take opioids or when there is no access to opioids for treatment of osteoarthritis pain	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	guidelines for at least 2 weeks, at any time, has not provided sufficient pain relief. • Participants who have intolerability or contraindications to NSAIDs/COX-2 inhibitors and opioids must have documented history that acetaminophen (paracetamol) within recommended dosing guidelines for at least 2 weeks, at any time, has not provided sufficient pain relief.	• ~~Participants who have intolerability or contraindications to opioids must have documented history that acetaminophen (paracetamol) and NSAID/COX-2 inhibitors treatment, either consecutively or simultaneously (including in combination products) within recommended dosing guidelines for at least 2 weeks, at any time, has not provided sufficient pain relief.~~ • ~~Participants who have intolerability or contraindications to NSAIDs/COX-2 inhibitors and opioids must have documented history that acetaminophen (paracetamol) within recommended dosing guidelines for at least 2 weeks, at any time, has not provided sufficient pain relief.~~		
5.2 Exclusion Criteria (General)	2. Previously received any form of anti-NGF, anti-TNF, or other biological DMARDs (including but not limited to golimumab, certolizumab, infliximab, adalimumab, etanercept, rituximab, abatacept, tocilizumab, and tofacitinib) for 12 months prior to screening or received other immunosuppressants for 6 months prior to screening	2. Previously received any form of anti-NGF, anti-TNF, or other biological DMARDs (including but not limited to golimumab, certolizumab, infliximab, adalimumab, etanercept, rituximab, abatacept, tocilizumab, and tofacitinib) ~~for~~ within 12 months prior to screening or received other immunosuppressants ~~for~~ within 6 months prior to screening (with the exception of inhaled or topical corticosteroids; for exclusionary intra-articular corticosteroids use, refer to exclusion criterion 37).	To clarify that the duration of the listed medications is not the important aspect for exclusion but the exposure relative to screening date; to clarify non-systemic corticosteroid use	Non-substantial
5.2 Exclusion Criteria (General)	None: new exclusion criterion	4. Administration of COVID-19 vaccine (regardless of modality or vaccine delivery platform, eg, vector, lipid nanoparticle) within 30 days prior to randomisation (from last vaccination or booster dose, whichever is required to consider vaccination complete in line with applicable guidance)	To reflect changes in the clinical study management of prospective study participants who may have access to COVID-19 vaccination	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
5.2 Exclusion Criteria (General)	5. Plasma donation within 28 days of screening or any blood donation or blood loss > 50 mL within 2 months of screening	6. Plasma donation within 28 days ~~of~~ prior to screening or any blood donation or blood loss > ~~50~~ 500 mL within 2 months ~~of~~ prior to screening	To clarify exclusion criterion; study team considers that it is appropriate to restrict blood loss to 500 mL within 2 months of screening; also minor correction in wording to increase clarity	Substantial
5.2 Exclusion Criteria (Medical History)	12. The following conditions (including screening imaging results suggestive of these conditions as per central reader evaluation) should be excluded: RPOA, primary osteonecrosis (including spontaneous osteonecrosis of the knee), subchondral insufficiency fractures, avascular necrosis, osteoporotic fractures, atrophic or hypotrophic OA, hip dislocation, excessive malalignment of the target knee or pathological fractures.	13. The following conditions (including screening imaging results suggestive of these conditions as per central reader evaluation) should be excluded: RPOA, primary osteonecrosis (including spontaneous osteonecrosis of the knee), subchondral insufficiency fractures, avascular necrosis, osteoporotic fractures, atrophic ~~or hypotrophic~~ OA, hip dislocation, congenital hip dysplasia with degenerative joint disease, excessive malalignment of the ~~target~~ knee (anatomical axis angle greater than 10 degrees), pathological fractures, stress fracture or reaction, vertical tear of the posterior meniscal root, or large or extensive subchondral cysts.	To clarify exclusionary conditions based on central reader's evaluation that represent joint pathology other than OA or have a potential impact on the accurate assessment of joint-related safety events	Substantial
5.2 Exclusion Criteria (Medical History)	23. Known or suspected systemic infection, including HIV, HBV, HCV, or TB should be excluded. If QuantiFERON test is positive at screening, participants will be excluded from the study. Other tests could be performed if deemed necessary by the investigators to exclude systemic infection.	24. Known or suspected systemic infection, including HIV, HBV, HCV, or TB should be excluded. If QuantiFERON test is positive at screening, participants will be excluded from the study. Other tests could be performed if deemed necessary by the investigators to exclude systemic infection. Note: Positive results for hepatitis B surface antigen (HBsAg) or antibody to hepatitis B core antigen (anti-HBc) are exclusionary.	To clarify exclusion criteria based on results from Hepatitis B testing	Non-substantial
5.2 Exclusion Criteria (Medical History)	30. Active infection and clinically important infection, including chronic, persistent, or acute infection within 3 months of screening or between screening and randomisation. Note that:	31. Current active infection, ~~and clinically important infection, including~~ chronic~~,~~ or persistent~~, or acute~~ systemic infection, or serious or severe localized or systemic infection within 3 months ~~of~~ prior to	To clarify exclusion criterion related to ongoing infections and	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	• Participants with clinical signs and symptoms consistent with COVID-19 infection or active COVID-19 infection and participants with a previous COVID-19 infection, irrespective of severity or symptomatology, are not eligible to participate in the study.	screening or between screening and randomisation. Note that: • ~~Participants with clinical signs and symptoms consistent with COVID-19 infection or active COVID-19 infection and participants with a previous COVID-19 infection, irrespective of severity or symptomatology, are not eligible to participate in the study.~~ • Any history of severe COVID-19 infection (eg, requiring hospitalisation, intensive care unit care, or assisted ventilation) or any prior COVID-19 infection with unresolved sequelae is exclusionary. Any acute SARS-COV-2/ COVID-19 infection, including asymptomatic, mild, or moderate (lab confirmed or suspected based on clinical symptoms) within the last 6 months prior to screening is also exclusionary.	infections in medical history	
5.2 Exclusion Criteria (Procedural Contraindications)	36. Corticosteroid injection or intra-articular hyaluronic acid injection on target knee within 6 months of screening or on a nontarget joint within 3 months of screening. If a participant has had multiple injections within the year prior to screening, then the total dose of corticosteroid used should be no more than 180 mg of triamcinolone, methylprednisolone, or their equivalent.	37. Corticosteroid injection or intra-articular hyaluronic acid injection on target knee within ~~6 months of~~ 12 weeks prior to screening, ~~or~~ corticosteroid injection on a nontarget joint within ~~3 months of~~ 12 weeks prior to screening, or intra-articular hyaluronic acid injection on nontarget joint within 6 weeks prior to screening. If a participant has had multiple injections within the year prior to screening, then the total dose of corticosteroid used should be no more than 180 mg of triamcinolone, methylprednisolone, or their equivalent.	Revision added as study team considers appropriate to reduce time elapsed from corticosteroid and hyaluronic acid intra-articular injection to screening	Substantial
5.2 Exclusion Criteria (Physical examination, vital signs, ECG, laboratory values, and imaging)	42. Orthostatic hypotension (defined as a sustained reduction of systolic BP of at least 20 mmHg and/or diastolic BP of at least 10 mmHg within 3 minutes of standing from a supine position)	43. Orthostatic hypotension (defined as a sustained reduction of systolic BP of at least 20 mmHg and/or diastolic BP of at least 10 mmHg within 3 minutes of standing from a supine position, provided that supine BP is stable). If supine BP results are not stable, the measurements can be repeated on the same day or at a subsequent screening visit. If it is not possible to	To clarify eligibility of the subjects for whom it is not possible to achieve a stable supine blood pressure for monitoring of orthostatic hypotension	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
		establish stable supine BP, then subject is not eligible for the study.		
5.2 Exclusion Criteria (Physical examination, vital signs, ECG, laboratory values, and imaging)	43. Any clinically significant abnormality in ECG rhythm, conduction, or morphology as judged by the investigator • A corrected QT interval by Fredericia (QTcF) interval measurement of > 470 microseconds or family history of long QT syndrome	44. Any clinically significant abnormality in ECG rhythm, conduction, or morphology as judged by the investigator • A corrected QT interval by Fredericia (QTcF) interval measurement of > 470 ~~microseconds~~ milliseconds or family history of long QT syndrome	To correct typo	Non-substantial
5.4.1 Rescreening	One rescreening visit is permitted within the 45-day screening period. Baseline X-ray and MRI assessments will remain valid for a maximum period of 45 days prior to Day 1. The following screening procedures should be performed at the rescreening visit: • X-ray/MRI if these have not been performed at screening • Recent medical history • Concomitant medications review • Physical examination • Neurological examination • 12-lead ECG • Screening pain NRS at the rescreening visit • TNSn • Vital signs and orthostatic BP • AEs • Urine drug screen • Laboratory tests (haematology, clinical chemistry, coagulation, serology, and pregnancy) A participant who is rescreened is not required to sign another ICF as the rescreening must occur within the 45-day screening period.	One rescreening attempt is permitted for each participant. For the participants who have undergone X-ray assessments during the screening period (and provided that there were no triggering events [eg, trauma] affecting the joints or any clinically significant changes in joint condition since the X-ray evaluation during the screening period based on the investigator's assessment), then rescreening, if deemed necessary, must occur within 90 days from this first screening X-ray assessment. If it is not possible to assess such changes in clinical condition over the above mentioned period, then the participants should not be rescreened. Note: There is no rescreening option beyond the above-mentioned 90 days for participants who have been exposed to X-rays during screening. For the study participants who were considered screen failures before any X-ray images were obtained, one rescreening attempt is allowed at any time point while the study is ongoing. All screening procedures and assessments (except for X-ray/MRI if performed at screening) should be repeated for the rescreened participants. A participant should sign a new ICF if they have been rescreened for any reason. ~~visit is permitted within the 45-day~~	To provide one rescreening opportunity for study participants	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
		~~screening period. Baseline X-ray and MRI assessments will remain valid for a maximum period of 45 days prior to Day 1.~~ ~~The following screening procedures should be performed at the rescreening visit:~~ • ~~X-ray/MRI if these have not been performed at screening~~ • ~~Recent medical history~~ • ~~Concomitant medications review~~ • ~~Physical examination~~ • ~~Neurological examination~~ • ~~12-lead ECG~~ • ~~Screening pain NRS at the rescreening visit~~ • ~~TNSn~~ • ~~Vital signs and orthostatic BP~~ • ~~AEs~~ • ~~Urine drug screen~~ • ~~Laboratory tests (haematology, clinical chemistry, coagulation, serology, and pregnancy)~~ ~~A participant who is rescreened is not required to sign another ICF as the rescreening must occur within the 45-day screening period.~~		
6.5.2 Prohibited Concomitant Medications	• Corticosteroid injections or intra-articular hyaluronic acid injections performed on the target knee within 6 months of screening are prohibited. Corticosteroid injections or intra-articular hyaluronic acid injections performed on a nontarget joint within 2 months of screening are prohibited.	• Corticosteroid injections or intra-articular hyaluronic acid injections ~~performed~~ on the target knee within ~~6 months of~~ 12 weeks prior to screening ~~are prohibited~~, corticosteroid injections ~~on a nontarget joint within~~ 12 weeks prior to screening, or intra-articular hyaluronic acid injections ~~performed~~ on a nontarget joint within ~~2 months of~~ 6 weeks prior to screening are prohibited.	To ensure consistency with exclusion criterion 37	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
6.5.2 Prohibited Concomitant Medications	• The following therapies are prohibited from 12 months prior to screening and during the study: ! Etanercept and medications known to interact with etanercept, specifically anakinra, abatacept, and sulfasalazine ! Other DMARDs, including but not limited to golimumab, certolizumab, infliximab, adalimumab, rituximab, tocilizumab, and ofacitinib ! Any other form of anti-TNF or anti-NGF therapy ! Other immunosuppressants with the exception of systemic corticosteroids that are prohibited from 6 months prior to screening and during the study.	• The following therapies are prohibited from 12 months prior to screening and during the study: ! Etanercept and medications known to interact with etanercept, specifically anakinra, abatacept, and sulfasalazine ! Other DMARDs, including but not limited to golimumab, certolizumab, infliximab, adalimumab, rituximab, tocilizumab, and tofacitinib ! Any other form of anti-TNF or anti-NGF therapy ! Other immunosuppressants ~~with the exception of systemic corticosteroids~~ ~~that~~ are prohibited from within 6 months prior to screening and during the study. The restrictions related to use of intra-articular corticosteroid injections are mentioned above.	To correct the discrepancy with the exclusion criterion related to immunosuppressants and corticosteroids use	Substantial
6.5.2 Prohibited Concomitant Medications	None: new bullet	• COVID-19 vaccines: If a study participant is being considered for enrolment into the study and also for COVID-19 vaccination, the participant must not be randomised until 30 days after the last dose of COVID-19 vaccine or 'booster dose' (whichever is required to consider vaccination complete in line with applicable guidance). Note that this is applicable only to COVID-19 vaccines, irrespective of their modality, which are currently approved by Health Authorities or otherwise approved under relevant regulations, eg, emergency use authorisation (FDA)/conditional marketing authorisation (European Medicines Agency)/temporary supply (Medicines and Healthcare Products Regulatory Agency).	To reflect changes in the clinical study management of prospective study participants who may have access to COVID-19 vaccination	Substantial
7.1 Discontinuation of	None: New bullet	• If a study participant is vaccinated with a COVID-19 vaccine during the treatment period of the study, he/she	To clarify discontinuation criteria	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
Investigational Product		should be discontinued from IP administration. The study participant will still be required to attend scheduled safety visits and to complete the follow-up period of the study (Please refer to Section 7.1.2 for "Procedures for Early Discontinuation of Investigational Product"). If a study participant is vaccinated during the follow-up period, they should continue participation in the follow-up period of the study.	for study participants receiving COVID-19 vaccination during the treatment or follow-up periods of the study	
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product	! A positive test for SARS-CoV-2 RNA at any time point	! A positive test for SARS-CoV-2 ~~RNA~~ at any time point	To provide more options for SARS-CoV-2 testing once new tests with acceptable standards would become available.	Non-substantial
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product	• Any of the following are criteria for immediate and permanent discontinuation of IP (Section 8.2.11.1): ! ALT or AST ≥ 5 × ULN ! ALT or AST ≥ 3 × ULN and coexisting total bilirubin ≥ 2 × ULN (Hy's Law [HL]). Hy's law is described in Section 8.3.8 and FU of HL cases is provided in Appendix F. ! ALT or AST ≥ 3 × ULN and associated with symptoms (which may be either transient or persistent) of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include eosinophilia (≥ 5%), rash, and fever without clear alternative cause.	• Any of the following are criteria for immediate and permanent discontinuation of IP (Section 8.2.11.1): ! ALT or AST ~~≥~~ > 5 × ULN for more than 2 weeks ! ALT or AST ≥ 3 × ULN and coexisting total bilirubin ≥ 2 × ULN (Hy's Law [HL]). Hy's law is described in Section 8.3.8 and FU of HL cases is provided in Appendix F. ! ALT or AST ≥ 3 × ULN and coexisting normalised ratio (INR) > 1.5 ! ALT or AST ≥ 3 × ULN and associated with symptoms (which may be either transient or persistent) of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include eosinophilia (≥ 5%), rash, ~~and~~ or fever without clear alternative cause.	To align with AstraZeneca's guidance for detection, assessment, and management of drug-induced liver injury	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
7.1.1 Subject-specific Criteria for Discontinuation of Investigational Product	None (new bullet)	! Cases when sympathetic neuropathy is not confirmed but orthostatic hypotension remains symptomatic for more than 14 days	To further clarify the language related to IP discontinuation criteria due to orthostatic hypotension when sympathetic neuropathy is not confirmed	Substantial
7.1.3 Temporary Discontinuation of Investigational Product	None (new bullet)	• When follow-up on cases of abnormal liver function is needed before the decision on permanent IP discontinuation is made (eg, identification of potential HL (PHL) cases needed or further evaluation in order to exclude HL required, or ALT or AST ≥ 5 × ULN for less than 2 weeks)	To provide guidance on temporary IP discontinuation before the decision about permanent IP discontinuation made	Substantial
7.1.3 Temporary Discontinuation of Investigational Product	None (new text)	Please refer to the Appendix F for guidance on follow-up procedures for PHL and HL cases and Section 8.2.11.1 for management of other cases of abnormal liver function	To indicate where (1) follow-up guidance for PHL and HL cases and (2) management of other cases of abnormal liver function are found in the CSP	Non-substantial
7.1.4 Procedures for Handling Incorrectly Enrolled or Randomised Subjects	A participant may be rescreened once and then be withdrawn if he/she still do not meet the eligibility criteria (Section 5.4.1). Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on IP, the investigator should inform the sponsor's study physician or designee immediately, and a discussion should occur between the study physician and the investigator. If the agreed decision is to discontinue IP, the participant will be asked to complete the assessments at the early termination visit and then enter the	A participant may be rescreened once and then be ~~withdrawn~~ screen failed if he/she still does not meet the eligibility criteria (Section 5.4.1). Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on IP, the investigator should inform the sponsor's study physician or designee immediately ~~and a discussion should occur between the study physician and the investigator~~. ~~If the agreed decision is to discontinue IP, the participant will be asked to complete the assessments at the early termination visit and then enter the follow-up~~	Minor revision and several sentences deleted to remove language that could indicate acceptance of protocol deviations	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	follow up period (Table 1). Procedures for early discontinuation of IP are provided in Section 7.1.2. The decision to discontinue/continue IP must be appropriately documented, including rationale, particularly if the agreed decision is to continue IP.	~~period (Table 1). Procedures for early discontinuation of IP are provided in Section 7.1.2.~~ ~~The decision to discontinue/continue IP must be appropriately documented, including rationale, particularly if the agreed decision is to continue IP treatment.~~		
8 Study Assessments and Procedures (Data reporting)	New text: new section added	**Data Reporting** The primary modality for study participants to capture daily information as well as complete all the study questionnaires during the study will be an ePRO hand-held device. In the event that there is a problem with the ePRO device or its availability, a digital alternative, electronic clinical outcomes assessment (eCOA) At-Home Web Back Up will be used for collecting eCOA data directly from patients when their provisioned device is not available.	To notify and provide guidance on the use of paper copies of the daily patient diary and questionnaires at the start of the study for collecting data until the ePRO devices become available for subject use	Non-substantial
8 Study Assessments and Procedures (Double-blind Treatment Period)	The following procedures will be performed on Day 1 prior to randomisation: • Inclusion and exclusion criteria confirmation • Urine pregnancy test (for women who are not surgically sterile only; the results must be negative in order to proceed with IP administration) • WOMAC index • Daily pain diary (NRS) • DSIS • Physical and neurological examination • Supine BP and pulse rate … • Orthostatic BP …) • Body temperature (prior to any blood draw) • Respiratory rate (prior to any blood draw) • ECG …	The following procedures will be performed on Day 1 prior to randomisation: • Inclusion and exclusion criteria confirmation • Urine pregnancy test (for women who are not surgically sterile only; the results must be negative in order to proceed with IP administration) • ~~WOMAC Index~~ • Daily pain diary (NRS) • DSIS • TNSn • Physical and neurological examination • Supine BP and pulse … • Orthostatic BP … • Body temperature (prior to any blood draw) • Respiratory rate (prior to any blood draw)	Move WOMAC and haematology/chemistry/ coagulation to after randomisation and pre-IP and TNSn to prior to randomisation because of the amount of time required to complete assessments	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	• Haematology/chemistry/coagulation • Urinalysis The following procedures will be performed on Day 1 after randomisation but prior to administration of IP: • TNSn • PGA • CCI • CCI • Survey of Autonomic Symptoms (SAS) • CCI • CCI • Blood for PK, ADAs, NGF, CXCL13, C… CCI	• ECG … • ~~Haematology/chemistry/coagulation~~ • Urinalysis The following procedures will be performed on Day 1 after randomisation but prior to administration of IP: • ~~TNSn~~ • WOMAC index • PGA • CCI • CCI • Survey of Autonomic Symptoms (SAS) • CCI • CCI • Blood for haematology/chemistry/coagulation, PK, ADAs, NGF, CXCL13, and CCI CCI		
8 Study Assessments and Procedures (Double-blind Treatment Period)	New language was added	On study Visit 4 (Day 14) and Visit 5 (Day 28), study participants will remain under observation for at least 2 hours after IP administration.	Added based on the recommendations made by the Danish Medicines Agency to provide longer onsite monitoring of potential acute reactions after the second and third CCI IP administration	Substantial
CCI				

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
			used in the SF-36; fixed in-text citation	
8.1.8 Assessment of Healthcare Resource Utilisation	The utilisation of healthcare resources (eg, doctor office visits, hospitalisations, surgeries, or other procedures) used by participants prior to entering the study (ie, 3 months prior to baseline) will be assessed at the times indicated in the SoA (Table 1). Healthcare resource utilisation data associated with medical encounters will be collected by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The question should be asked with a recall period of 3 months.	The utilisation of healthcare resources (eg, doctor office visits, hospitalisations, surgeries, or other procedures) used by participants prior to entering the study (ie, 3 months prior to baseline) and during the study will be assessed at the times indicated in the SoA (Table 1). Healthcare resource utilisation data associated with medical encounters will be collected by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. After the baseline assessment, the question should be asked ~~with a recall period of 3 months~~ by recalling the period between visits.	To increase objectivity and accuracy of recall period by reducing recall period to the period between visits.	Non-substantial
8.2.3.2 Orthostatic Blood Pressure Measurements and Follow-up of Confirmed Orthostatic Hypotension	If the BP measurements do not meet the criteria for orthostatic hypotension, no additional measurement is needed. If the BP measurement meets any of the criteria shown in Table 6, investigators will repeat the supine and standing measurements up to 2 additional times.	If the BP measurements do not meet the criteria for orthostatic hypotension, no additional measurement is needed (refer to exclusion criterion 43 for screening visit and Visit 2 assessments and Table 6 for the assessments after Visit 2). If BP measurements taken at the screening visit or Visit 2 meet exclusion criterion 43, then the subject in not eligible for participation in the study. After Visit 2 (Day 1), if the initial BP measurement meets any of the criteria shown in Table 6, investigators will repeat the supine and standing measurements up to 2 additional times.	To clarify when orthostatic blood pressure measurements outlined in the Table 6 and follow-up of confirmed orthostatic hypotension are applicable	Non-substantial
8.2.6.1 Radiographic (X-ray) Assessment	Details of the image acquisition and review criteria will be described in the Radiology Technical Manual.	Details of the image acquisition ~~and review criteria~~ will be described in the ~~Radiology Technical Manual~~ Procedure Manuals for X-ray and MRI Image Acquisition.	To align with the title and content of manuals for X-ray and MRI image acquisition	Non-substantial
8.2.6.2 Magnetic Resonance Imaging	MRI of the bilateral knee joints must be done during the screening period (Table 1). An MRI should also be performed during the screening period for the	MRI of the bilateral knee joints must be done during the screening period (Table 1) except for the cases when a study participant has undergone a total joint	#1: To clarify that MRI should not be obtained	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	joints with a KL grade at baseline of ≥ 3 as per screening X-ray assessment. Eligibility (absence of specified joint abnormalities) will be determined by a central imaging reader. In addition, unscheduled MRIs should be done "for cause" in the knee joints or the joints with a KL grade at baseline of ≥ 3 to follow up on any newly occurring symptoms or worsening of symptoms considered clinically significant by the investigator.	replacement and has an artificial nontarget joint or when a knee joint is no longer present due to leg amputation. In that case only acquire MRI images of the opposite (target) knee. An MRI should also be performed during the screening period for the joints with a KL grade at baseline of ≥ 3 as per screening X-ray assessment. Eligibility (absence of specified joint abnormalities) will be determined by a central imaging reader. In addition, unscheduled MRIs should be done "for cause" in the knee joints or the joints with a KL grade at baseline of ≥ 3 to follow up on any newly occurring symptoms or worsening of symptoms considered clinically significant by the investigator (except for the cases when a study participant has undergone a total joint replacement and has an artificial joint).	for nontarget knee with an artificial joint #2: To clarify that MRI should not be obtained for an artificial joint	
8.2.6.2 Magnetic Resonance Imaging	Details of the image acquisition and review criteria will be described in the Radiology Technical Manual.	Details of the image acquisition ~~and review criteria~~ will be described in the ~~Radiology Technical Manual~~ Procedure Manuals for X-ray and MRI Image Acquisition	To align with the titles of the site manuals for X-ray and MRI image acquisition.	Non-substantial
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests	**Table 8** AST or ALT: ≥ 3 × ULN Total bilirubin: ≥ 2 × ULN Symptom of hepatitis or hypersensitivity: NA Consultation required: Hepatology consultation [d]; Case must be discussed with the medical monitor ASAP Actions: Immediate and permanent discontinuation of IP Tests: Essential: must have liver chemistry values and additional testing completed ASAP	**Table 8** AST or ALT: ≥ 3 × ULN Total bilirubin: ≥ 2 × ULN Symptom of hepatitis or hypersensitivity: NA Consultation required: Hepatology consultation [d]; Case must be discussed with the medical monitor ASAP Actions: Immediate and permanent discontinuation of IP Tests: Essential: must have liver chemistry values and additional testing completed ASAP (Appendix F7) or	To clarify that follow-up on PHL cases is also needed as per Appendix F	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	(Appendix F7) or follow up events of Hy's law, if applicable as per Appendix F4) Evaluation: Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]	follow-up events of PHL or HL, if applicable as per Appendix F-~~4~~) Evaluation: Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]		
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests	**Table 8** AST or ALT: ≥ 3 × ULN Total bilirubin: NA Symptom of hepatitis or hypersensitivity: Yes Consultation required: Hepatology consultation [d]; Case must be discussed with the medical monitor ASAP Actions: Immediate and permanent discontinuation of IP Tests: Essential: must have liver chemistry values and additional testing completed ASAP (Appendix F7) or follow up events of Hy's law, if applicable as per Appendix F4) Evaluation: Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]	**Table 8** AST or ALT: ≥ 3 × ULN Total bilirubin: NA Symptom of hepatitis or hypersensitivity: Yes Consultation required: Hepatology consultation [d]; Case must be discussed with the medical monitor ASAP Actions: Immediate and permanent discontinuation of IP Tests: Essential: must have liver chemistry values and additional testing completed ASAP (Appendix F7) or follow-up events of PHL or HL, if applicable as per Appendix F-~~4~~) Evaluation: Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]	To clarify that follow-up on PHL cases is also needed as per Appendix F	Non-Substantial
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests	**Table 8** AST or ALT: ≥ 5 × ULN Total bilirubin: NA Symptom of hepatitis or hypersensitivity: NA Consultation required: Hepatology consultation [d]; Case must be discussed with the medical monitor ASAP	**Table 8** AST or ALT: ≥ 5 × ULN Total bilirubin: ~~NA~~ < 2 × ULN [f] Symptom of hepatitis or hypersensitivity: ~~NA~~ No Consultation required: ~~Hepatology consultation~~ [d]; Case must be discussed with the medical monitor ASAP Actions: Immediate ~~and permanent~~ IP discontinuation ~~of IP~~ required; Permanent IP discontinuation required	To align with AstraZeneca's guidance for detection, assessment, and management of drug-induced liver injury	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	Actions: Immediate and permanent discontinuation of IP Tests: Essential: must have liver chemistry values and additional testing completed ASAP (Appendix F7) or follow up events of Hy's law, if applicable as per Appendix F4) Evaluation: Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]	if follow-up tests reveal AST or ALT ≥ 3 × ULN and INR > 1.5, or ALT or AST > 5 × ULN for more than 2 weeks Tests: Essential: Must have liver chemistry values and additional testing completed ASAP (Appendix F7) ~~or follow up events of Hy's law, if applicable as per Appendix F4)~~ Evaluation: Hepatology consultation [d]; Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]		
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests	**Table 8** AST or ALT: ≥ 3 × ULN (and ≥ 2 × baseline) and < 5 × ULN Total bilirubin: < 2 × ULN Symptom of hepatitis or hypersensitivity: No Consultation required: Discussion with medical monitor required Actions: Immediate discontinuation of IP not required unless deemed necessary by the investigator Tests: Not required unless otherwise medically indicated (at the discretion of the investigator) Evaluation: Monitoring of liver chemistry values at least twice per week until values normalise, stabilise, or return to within baseline level [e]	**Table 8** AST or ALT: ≥ 3 × ULN (and ≥ 2 × baseline) and < 5 × ULN Total bilirubin: < 2 × ULN [f] Symptom of hepatitis or hypersensitivity: No Consultation required: Discussion with medical monitor required Actions: Temporal ~~Immediate~~ IP discontinuation ~~of IP~~ needed for the period required for obtaining ~~not required unless~~ repeated liver function tests and INR. Permanent discontinuation of IP required if follow-up tests reveal AST or ALT ≥ 3 × ULN and INR > 1.5 or as deemed necessary by the investigator Tests: Measure ALT, AST, ALP, GGT, and bilirubin (total and direct), INR, albumin in 48-72 hours. Other tests might be performed as ~~Not required unless otherwise~~ medically indicated (at the discretion of the investigator) Evaluation: If the tests reveal AST or ALT ≥ 3 × ULN and INR > 1.5, then hepatology consultation and monitoring of liver chemistry values required at least	To align with AstraZeneca's guidance for detection, assessment, and management of drug-induced liver injury	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
		twice per week until values normalise, stabilise, or return to within baseline level		
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests	None (new footnote)	[f] All bilirubin values since the start of IP exposure should be checked to exclude PHL criteria (Appendix F2). If the PHL criteria are met, IP should be immediately discontinued, and the case needs to be reported and followed-up as per guidance in Appendix F.	Wording added to ensure that potential HL cases are not missed	Non-substantial
8.2.11.1 Guidance for Evaluation of Abnormal Liver Function Tests	The criteria below makes provision for the continuation of IP treatment at the discretion of the investigator. • Participants with ALT or AST ≥ 3 × ULN (and ≥ 2 × baseline) and < 5 × ULN, total bilirubin < 2 × ULN with no symptoms of hepatitis (Table 8).	The criteria below makes provision for the continuation of IP treatment at the discretion of the investigator. • Participants with ALT or AST ≥ 3 × ULN (and ≥ 2 × baseline) and < 5 × ULN, total bilirubin < 2 × ULN and INR ≤ 1.5 with no symptoms of hepatitis or hypersensitivity (Table 8).	Minor changes to align with Table 8	Non-substantial
8.3.5 Adverse Events of Special Interest	An AESI is an AE of scientific and medical interest specific to understanding of the effects of the IP and may require close monitoring …	An AESI is ~~an~~ a treatment-emergent AE of scientific and medical interest specific to understanding of the effects of the IP and may require close monitoring …	To clarify definition of an AESI	Non-substantial
8.3.5 Adverse Events of Special Interest	The following AESIs have been identified specifically for this MEDI7352 protocol and are to be reported as described in Section 8.3.1 to Section 8.3.4. • Positively-adjudicated possible or probable RPOA, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture • ~~Systemic infections~~ • Anaphylactic reactions and injection site reactions that lead to discontinuation of administration of IP Adverse events of special interest irrespective of their severity should be reported immediately using the same procedure as for SAE reporting (Section 8.3.9.)	The following AESIs have been identified specifically for this MEDI7352 protocol and are to be reported as described in Section 8.3.1 ~~to~~ through Section 8.3.4. • Positively-adjudicated possible or probable RPOA, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture • ~~Systemic infections~~ • Infections that meet SAE or severe AE criteria* • Anaphylactic reactions and injection site reactions that lead to 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 8.3.9).	To further clarify infection-related AESI	Substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
		*Note: A serious infection is any infection that meets the SAE criteria in CSP Appendix C2 "Definition of Serious Adverse Event." 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.		
8.3.9 Reporting of Serious Adverse Events	All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the eCRF. If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representative within one day, ie, immediately but no later than 24 hours of when he or she becomes aware of it by completing, signing, and dating the SAE Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to AstraZeneca representative. • Email: drugsafety@mmsholdings.com • Fax number: +1 734 468 0850 The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site-**within one calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.	All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the eCRF. If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representative within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it by completing the appropriate forms in the electronic data capture (EDC) system and submitting electronically to the safety team. Any follow-up information received must also be updated within the system and resubmitted within 24 hours of being made aware. SAE reporting via paper forms will only serve as backup if the EDC system were to be temporarily unavailable for any unforeseen reasons. In such cases, the electronic SAE form can be completed within the EDC system when it becomes available. This will ensure safety events are still reported within 24 hours of any site staff being made aware. The paper SAE report forms are available in the investigator site files and must be completed by the principal investigator by signing, and dating the SAE Report Form, verifying the accuracy of the information recorded in the form with the source	To clarify that SAE reporting process; SAEs will be reported via EDC, not paper reporting.	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
		documents and eCRF, and sending the SAE form to the AstraZeneca representative. • Email: drugsafety@mmsholdings.com • Fax number: +1 734 468 0850 The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **or representative within one calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.		
8.3.10 Pregnancy	A woman who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately withdrawn from study participation. The investigator must report the pregnancy to AstraZeneca or representative as if it were an SAE within 24 hours of learning of the pregnancy using the pregnancy notification and outcome form via the same fax number and/or email address as for SAE reporting. All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca or representative. • Email: drugsafety@mmsholdings.com • Fax number: +1 734 468 0850 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 FU information must be reported to AstraZeneca or	A woman who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately withdrawn from study participation. The investigator must report the pregnancy to AstraZeneca or representative as if it were an SAE (within 24 hours of learning of the pregnancy) ~~using the pregnancy notification and outcome form.~~ by completing the appropriate forms in the EDC system and submitting electronically to the safety team. Pregnancy reporting via paper forms will only serve as backup if the EDC system were to be temporarily unavailable for any unforeseen reasons, as described in Section 8.3.9. The paper pregnancy notification and outcome forms are available in the investigator site files. All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca or representative via the EDC system. If paper pregnancy notification and outcome forms are used as backup, these must be completed by the principal investigator, and sent via the same fax number and/or email address as for SAE reporting	To clarify pregnancy reporting process	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
	representative using a new pregnancy notification and outcome form.	• Email: drugsafety@mmsholdings.com • Fax number: +1 734 468 0850 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 FU information must be reported to AstraZeneca or representative (MMS) by submitting ~~using~~ a ~~new~~ pregnancy notification and outcome EDC report form.		
8.3.10.1 Maternal Exposure	Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca or its representative.	Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca or its representative via the EDC system.	To clarify pregnancy reporting process	Non-substantial
8.3.10.2 Paternal Exposure	Pregnancy in a participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose of IP until 3 months and 20 days after the last dose of IP should, if possible, be followed up and documented in the pregnancy report form. Consent from the partner must be obtained before the pregnancy report form is completed.	Pregnancy in a participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose of IP until 3 months and 20 days after the last dose of IP should, if possible, be followed up and documented in the pregnancy EDC report form. The site will update the information within the EDC system and submit to AstraZeneca or representative (MMS). Consent from the partner must be obtained before the pregnancy report form is completed.	To clarify pregnancy reporting process	Non-substantial
8.4 Overdose	The maximal dose of IP should not be exceeded during the study. The investigator must report any overdose to an AstraZeneca representative within 24 hours of learning of the overdose using the overdose report form.	The maximal dose of IP should not be exceeded during the study. The investigator must report any overdose to an AstraZeneca representative within 24 hours of learning of the overdose ~~using the overdose report form~~ by completing the appropriate forms in the EDC system and submitting electronically to the safety team. Drug overdose reporting via paper forms will only serve as backup if the EDC system were to be	To clarify overdose reporting process	Non-substantial

Section # and Name	Initial Wording under Version 1	Amended or New Wording under Amendment 1	Brief Rationale	Substantial/ Non-substantial
		temporarily unavailable for any unforeseen reasons, as described for SAE reporting (Section 8.3.9). The paper forms are available in the investigator site files and must be completed by the principal investigator.		
9.4.3.1 Adverse events	Treatment-emergent AEs are defined as: • AEs with onset at the time of or following the start of IP through the FU visit or ET visit, whichever occurs first, or • AEs starting prior to the start of IP administration but increasing in severity or relationship at the time of, or following, the start of IP through the FU visit or ET visit, whichever occurs first,	Treatment-emergent AEs are defined as: • AEs with onset at the time of or following the start of IP through the ~~FU~~ last visit ~~or ET visit, whichever occurs first, or~~ • AEs starting prior to the start of IP administration but increasing in severity or relationship at the time of, or following, the start of IP through the ~~FU~~ last visit ~~or ET visit, whichever occurs first,~~	To simplify language and increase clarity	Non-substantial
Appendix B 3 Informed Consent	A participant who is rescreened is not required to sign another ICF as the rescreening must occur within the 45-day screening period.	A participant who is rescreened is ~~not~~ required to sign ~~another~~ a new ICF ~~as the rescreening must occur within the 45-day screening period.~~	To clarify and to be consistent with changes in the rescreening section	Non-substantial
Appendix B 5 Committees Structure	**Rapidly Progressive Osteoarthritis Adjudication Committee** The role of the Rapidly Progressive Osteoarthritis Adjudication Committee (RPOA-AC) is to independently review, interpret, and adjudicate possible or probable joint safety events including but not limited to RPOA, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture cases that are experienced by the study participants. The adjudication committee will review all cases of suspected joint safety events to determine whether or not they meet accepted diagnostic criteria. The RPOA-AC will review and adjudicate all joint safety events that meet SAE or severe AE criteria or AEs that led to joint replacement or other arthroplasty procedures. Joint safety events will be identified preliminarily by the	**Rapidly Progressive Osteoarthritis Adjudication Committee** The role of the Rapidly Progressive Osteoarthritis Adjudication Committee (RPOA-AC) is to independently review, interpret, and adjudicate possible or probable joint safety events including but not limited to RPOA, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture cases that are experienced by the study participants. ~~The adjudication committee will review all cases of suspected joint safety events to determine whether or not they meet accepted diagnostic criteria.~~ The RPOA-AC will review and adjudicate all joint safety events that meet SAE or severe AE criteria or AEs that led to joint replacement or other arthroplasty procedures to determine whether or not they meet accepted diagnostic criteria. Joint safety events will be identified	Redundant sentence removed as joint safety events that will be reviewed by RPOA-AC are specified: RPOA, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture and all joint safety events that meet SAE or severe AE criteria or AEs that led to joint replacement or other arthroplasty procedures	Non-substantial

<table>
<tr><th>Section # and Name</th><th>Initial Wording under Version 1</th><th>Amended or New Wording under Amendment 1</th><th>Brief Rationale</th><th>Substantial/ Non-substantial</th></tr>
<tr><td></td><td>investigators, and also by AstraZeneca/sponsor personnel or during the RPOA-AC process as specified in the committee’s charter.</td><td>preliminarily by the investigators, and also by AstraZeneca/sponsor personnel or during the RPOA-AC process as specified in the committee’s charter.</td><td></td><td></td></tr>
<tr><td>Appendix B 10 Publication Policy</td><td>The results of this study may be published or presented at scientific meetings. The investigator must agree to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.</td><td>The results of this study may be published or presented at scientific meetings. Publications developed and managed by the investigator will be shared with the sponsor for review and approval before submission. ~~The investigator must agree to submit all manuscripts or abstracts to the sponsor before submission.~~ This allows the sponsor to review the publication for accuracy and to ensure ~~protect~~ any proprietary information is protected. ~~and to provide comments.~~</td><td>Revised in response to German Ethics Committee (EC) query as to clarify that the purpose of the publication policy is to identify and remove any proprietary information from the publication</td><td>Non-substantial</td></tr>
<tr><td>Appendix I Summary of Imaging Assessments (Table I11)</td><td><table><tr><th colspan="3">Imaging Assessments to be Performed During the Study</th></tr><tr><th>Joints/ indications</th><th>X-ray (plain radio-graphs</th><th>MRI</th></tr><tr><td>Shoulders (both)</td><td>E and S</td><td>for joints with KL grade 3 or more</td></tr></table></td><td><table><tr><th colspan="3">Imaging Assessments to be Performed During the Study</th></tr><tr><th>Joints/ indications</th><th>X-ray (plain radiographs)</th><th>MRI</th></tr><tr><td>Shoulders (both)</td><td>E and S</td><td>~~for joints with KL grade 3 or more~~ When further clarification of imaging findings needed</td></tr></table></td><td>To clarify that MRI of shoulder joints will be performed only when deemed necessary based on central reader evaluation of X-ray data and when it is clinically indicated during the study (due to issues with accurate definition of KL grade 3 in shoulder joints)</td><td>Non-substantial</td></tr>
</table>

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<tr><th>Section # and Name</th><th>Initial Wording under Version 1</th><th>Amended or New Wording under Amendment 1</th><th>Brief Rationale</th><th>Substantial/ Non-substantial</th></tr>
<tr><td>Appendix I
Summary of Imaging Assessments
(Table I12)</td><td>
<table>
<tr><th colspan="4">Schedule of Assessments - Imaging</th></tr>
<tr><th>Imaging</th><th>Knee</th><th>Hip</th><th>Shoulder</th></tr>
<tr><td>MRI</td><td>Both knee joints at screening and as clinically indicated during the study</td><td>Joints with KL grade 3 or more at screening and as clinically indicated during the study</td><td>For joints with KL grade 3 or more at screening and as clinically indicated during the study</td></tr>
</table>
</td><td>
<table>
<tr><th colspan="4">Schedule of Assessments - Imaging</th></tr>
<tr><th>Imaging</th><th>Knee</th><th>Hip</th><th>Shoulder</th></tr>
<tr><td>MRI</td><td>Both knee joints at screening and as clinically indicated during the study</td><td>Joints with KL grade 3 or more at screening and as clinically indicated during the study</td><td>~~For joints with KL grade 3 or more at screening and~~ As clinically indicated during the study</td></tr>
</table>
</td><td>To clarify that MRI of shoulder joints will be performed only when clinically indicated during the study</td><td>Non-substantial</td></tr>
</table>

Abbreviations are found in Appendix L.

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