Clinical Study Report Synopsis	
Drug Substance	MEDI7352
Study Code	D5680C00002
Edition Number	CSR Version 1
Date	31 January 2024
EudraCT Number	2018-002523-42
NCT Number	NCT03755934

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

Study dates:
First subject enrolled: 27 November 2018
Last subject last visit: 29 June 2023
The analyses presented in this report are based on a clinical data lock date of 31 August 2023

Phase of development:
Therapeutic exploratory (II)

Sponsor's Responsible Medical Officer:
PPD
AstraZeneca plc
Cambridge Biomedical Campus - DISC
1 Francis Crick Avenue, Cambridge, CB2 0AA

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 48 sites in 6 countries (the United Kingdom, Hungary, Poland, Romania, Denmark, and Spain). No subjects were enrolled in Denmark: 1 subject was screened at the only site in Denmark, who failed screening. No subjects were enrolled in Spain; 2 sites were activated but did not enrol subjects.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and endpoints are presented in Table S1.

Table S1 Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of MEDI7352 versus placebo on chronic pain in subjects with PDN currently taking standard of care medication for their PDN pain	Primary: • Change in the weekly average of the average daily pain scores from the baseline week to Week 12 of MEDI7352 compared to placebo, as measured on an 11-point (0 to 10) NRS Secondary: • Change in the weekly average of the average daily pain score, as measured on an 11-point (0 to 10) NRS, from baseline to Weeks 2, 4, 6, 8, and 10 of treatment and the week before the follow-up visit • Percentage of subjects who have achieved ≥30% and ≥50% reductions in the weekly average of the average daily pain score from baseline during Weeks 4, 8, and 12 of treatment and the week before follow-up • Change in Galer Neuropathic Pain Scale from baseline to Days 28, 56, and 84 of treatment and the follow-up visit • Change in Daily Sleep Interference Scale from baseline to Days 28, 56, and 84 of treatment and the follow-up visit • Proportion of subjects who have 'improved', 'much improved', or 'very much improved' relative to baseline on the Patient Global Impression of Change on Days 28, 56, and 84 of treatment and the follow-up visit • Change in the 36-Item Short-form Health Survey from baseline to Day 84 of treatment • Change in the amount of rescue medication used (in terms of dosage/day) from baseline to Week 12 of treatment

Objectives	Endpoints
Secondary	
• To assess the safety and tolerability of MEDI7352 in subjects with PDN	• Safety and tolerability assessments: AEs and serious AEs, physical and neurological examinations, neuropathy assessments (Total Neuropathy Score-Nurse), strength (dorsiflexion) and deep tendon reflex (knee and ankle) assessments, vital signs, 12-lead electrocardiograms, clinical laboratory testing (haematology, clinical chemistry, coagulation, and urinalysis), motor and sensory nerve conduction, concomitant medication assessment, injection-site reaction assessment, and infusion reaction assessments
• To assess the pharmacokinetic, pharmacodynamic, and immunogenicity of MEDI7352 in subjects with PDN	• Primary pharmacokinetic parameters of MEDI7352 included C_{max}, time of C_{max}, area under the serum concentration-time curve from time 0 to infinity, area under the serum concentration-time curve from time 0 to the time of the last quantifiable serum concentration, area under the serum concentration-time curve for the dosing interval at steady state, C_{max} at steady state, volume of distribution at steady state, half-life, and total body clearance at steady state[a] • Pharmacodynamics: Free and/or total nerve growth factor measurements in serum/plasma • Immunogenicity (anti-drug antibody) assessments
• To characterise the dose-response relationship of MEDI7352 on chronic pain in subjects with PDN	• Change in the weekly average of the average daily pain scores from the baseline week to Week 12, as measured on an 11 point (0 to 10) NRS, versus dose

Abbreviations: AE = adverse event; C_{max} = maximum concentration; NRS = Numeric Rating Scale; PDN = painful diabetic neuropathy

a In the protocol, this parameter was listed as "apparent" total body clearance at steady state; however, as the route of administration of MEDI7352 in this study was IV, the term "apparent" is not correct. Note: Exploratory objectives and endpoints are described in the clinical study report.

Study design

This was a randomised, double-blind, placebo-controlled, multicentre study of MEDI7352 in subjects with moderate to severe chronic painful diabetic neuropathy (PDN) persistent for 6 months or longer, not adequately controlled by standard of care treatments, caused by type 1 or type 2 diabetes mellitus. The study incorporated a screening period of up to 45 days and a 12week double-blind treatment period during which MEDI7352 or placebo was administered intravenously on 6 occasions, with each dose separated by 14 days. There was a 6-week follow-up period.

Four stages were planned in the study. As described in the protocol, subjects in the first stage were to be randomly assigned to placebo or the lowest dose of MEDI7352 CCI until at least 10 subjects had been recruited. In the second stage, up to a maximum of 30 subjects were to be randomly assigned to placebo or MEDI7352 CCI. In stage 3 of the study, approximately 67 subjects were planned to be randomly assigned to placebo or MEDI7352 CCI to ensure that sufficient subjects were evaluable for the pre-planned interim

analysis. Administrative analyses were also conducted during the third stage of the study to confirm decision making for stage 4 with respect to the exact sample size and dose allocation ratio. Upon completing enrolment in stage 3, an interim analysis was to be performed, and stage 4 was to be conducted; approximately 165 eligible subjects were planned to be randomly assigned to treatment with equal allocation across 3 dose levels of MEDI7352 or placebo in stage 4, to ensure that approximately 236 subjects were evaluable for the efficacy analysis of stages 2 to 4 combined. The randomisation schedule was computer generated using a permuted block algorithm appropriate to the treatment groups included in each stage and randomly allocated investigational product (IP) to randomisation numbers.

After all subjects in stage 3 completed the study, the sponsor decided to prematurely terminate the study due to longer enrolment than was anticipated. It was concluded that progressing with the current protocol to stage 4 would be challenging. The sponsor halted screening activities on 12 January 2023 and informed the sites about the termination of the study on 11 April 2023. Ongoing subjects continued on treatment until the end of the study and the required follow up period as per protocol. Afterwards the database was cleaned, locked, final analysis was performed, and the final clinical study report (CSR) was prepared.

Target population and sample size

Key inclusion criteria:

- male, or post-menopausal or surgically sterile females;
- 18 to 80 years of age (inclusive) on the day of randomisation;
- a body mass index of ≤42 kg/m^2;
- chronic PDN persistent for 6 months or longer that was not adequately controlled by standard of care treatments;
- a mean pain intensity score of ≥4, as measured on an 11-point (0 to 10) Numeric Rating Scale (NRS);
- be willing and able to discontinue all nonsteroidal anti-inflammatory drug or cyclooxygenase2 analgesic therapy;
- had to be taking medication for the treatment of PDN. Subjects had to be taking at least 1 of the first-line medications (consistent with regional or local standard of care guidelines for PDN) belonging to either the anticonvulsant class (pregabalin or gabapentin) or the antidepressant class (duloxetine, venlafaxine, or amitriptyline), but no more than 1 medication from a single class.

Key exclusion criteria:

- other clinically significant neuropathy;
- clinically significant osteoarthrosis;
- other chronic pain conditions;
- major psychiatric disorders;
- significant cardiovascular or lung disease;

- clinically important infections;
- other serious illnesses.

Approximately 272 eligible subjects were planned to be randomly assigned to double-blind treatment with 1 of 4 dose levels of MEDI7352 (CCI dependent upon the stage of the study) or placebo to ensure that approximately 236 subjects were eligible for the efficacy analysis of stages 2, 3, and 4 combined. There was no formal sample size calculation for stage 1; 10 subjects in stage 1 were considered sufficient for the initial assessment of safety. The sample size for stages 2 to 4 combined was determined by a formal power calculation (see below) and the size of stage 3 was defined to confirm decision making for the stage 4 sample size and dose allocation ratio.

This study was powered at greater than 80% to detect a statistically significant (1-sided alpha = 0.025) dose-response relationship when the true Week 12 placebo-corrected change from baseline (CFB) difference at the CCI dose was 1.25 on the 11-point NRS scale (MEDI7352-placebo treatment) and the true dose-response followed a hyperbolic maximum effect of the drug (E_{max}) relationship, with the dose to achieve 50% of the maximum effect (ED50) within the range of 1 to 750 µg/kg. This calculation also assumed:

- The true standard deviation (SD) was 2.4, which was based on other studies undertaken with pregabalin in PDN.
- The data from stages 2, 3, and 4 would be combined so that the number of subjects evaluable for the dose-response analysis was 236. The total number of subjects evaluable for efficacy for the placebo, CCI doses of MEDI7352 would be equal to 81, 37, 51 and 67, respectively.
- The dose-response hypothesis test was multiplicity adjusted in order to control the type 1-error.

The above calculations were performed using the following parameters:

- Population SD (of CFB to week 12) = 2.4
- Placebo effect = 1-point reduction in NRS and CCI effect = 2.25 reduction from baseline, ie, delta = 1.25
- Linear contrasts were determined from 5 ‘candidate dose’ response models which are all E_{max} models with decreasing potency/increasing ED50: 7.5, 15, 30, 60, 750 µg/kg. The 5th case was essentially linear in dose.
- Power was assessed across 16 alternative true dose-response curves, 12 E_{max} with ED50 ranging from 0.375 to 750 µg/kg, 3 logistic and 1 quadratic, all having a Week 12 placebo-corrected CFB difference at the CCI dose of 1.25.

The overall withdrawal rate was anticipated to be approximately 10%. However, since the primary analysis used last observation carried forward (LOCF) for withdrawn subjects, and the SD estimate was taken from studies which also used the LOCF approach, the only

additional subjects recruited were to account for withdrawals in stages 2, 3, and 4 if withdrawal occurred at, or prior to, the Week 2 visit.

Investigational product and comparator(s): dosage, mode of administration, and batch/lot numbers

The IP in this study was MEDI7352. It was administered at dose levels of CCI [redacted] with the study being terminated before stage 4, a planned CCI [redacted] dose was not evaluated. Each subject was to receive 6 doses, 1 dose every 2 weeks (Days 1, 14, 28, 42, 56, and 70), administered intravenously over a 60-minute period. The batch/lot numbers were as follows: batch number CCI [redacted] lot/packaging number CCI [redacted] lot/packaging number CCI [redacted] lot/packaging number CCI [redacted].

Placebo was the control product in this study. The placebo comprised of intravenous bag protectant (IVBP) added to 0.9% (w/v) sodium chloride solution for infusion. The IVBP was used to preserve blinding as IVBP may produce a small amount of foam in the IV bag. The dose levels, route, and frequency of use was the same as for MEDI7352. The batch/lot numbers were as follows: CCI [redacted] lot/packaging number CCI [redacted] lot/packaging number CCI [redacted] lot/packaging number CCI [redacted] lot/packaging number CCI [redacted].

Duration of treatment

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

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

The maximum treatment duration for each subject was approximately 12 weeks. The maximum study duration for each subject was approximately 25 weeks.

Statistical methods

The following 4 analysis populations were planned for this study:

- Screening: all subjects who provided informed consent and/or assent and provided demographic and/or baseline screening assessments, regardless of the subject's randomisation and treatment status in the study.
- Safety: the safety population included all subjects who received at least 1 dose of double-blind study medication.
- Modified intent-to-treat (mITT): the mITT population was used for all efficacy analyses and included all randomised subjects who received at least 1 dose of double-blind study medication and had at least 1 post-baseline NRS assessment.

- Pharmacokinetic (PK): the PK population included all subjects for whom a PK sample was obtained and analysed. Subjects receiving placebo were not included in the summary and analysis of PK parameters.

Subject characteristics and disposition

Baseline subject characteristics were listed and included in summaries as appropriate. Investigational product administration was summarised in terms of each subject's total dose and number of infusions received using descriptive statistics.

Efficacy analyses

All efficacy variables were 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 were tabulated according to the 'observed cases' approach. In addition, if there were missing data at a key analysis time point (Weeks 4, 8, and 12) then results were also tabulated according to LOCF and baseline observation carried forward (BOCF). The main statistical analysis of the primary efficacy endpoint at Week 12 used the multiple comparison procedure modelling approach on LOCF data, which is a well-established statistical methodology for establishing both the existence of a dose response and modelling the underlying dose-response relationship. In addition, changes from baseline in continuous endpoints were compared between treatment groups using mixed models for repeated measures including terms for treatment (as a factor), time point (as a factor), the interaction between treatment and time point, and the baseline value of the variable undergoing analysis. Binary outcomes were analysed using generalised estimating equations, with the models including the same terms as the mixed models repeated measures. Other non-binary categorical endpoints were analysed using Cochran-Mantel-Haenszel statistics. These analyses were conducted on observed cases. Further details of the longitudinal modelling are included in the statistical analysis plan (SAP).

Clinical pharmacology analyses

The PK endpoints involving derivation of PK parameters for each dose and for each subject by noncompartmental analysis were replaced by a combined population PK analysis of data from multiple MEDI7352 studies including this study. This is documented in the SAP and in the CSR as a change in planned analysis. The combined data analysis is described in a separate pharmacometrics analysis plan. As a result, description of tables, listings, and figures related to PK parameters were removed from the SAP.

Pharmacodynamic (PD) and immunogenicity: the PD variable (total nerve growth factor) and immunogenicity data were summarised using descriptive statistics and were listed.

Pharmacogenetic analysis

Analysis of pharmacogenetics data was described in a separate analysis plan.

Safety analyses

Safety and tolerability data were summarised descriptively, including tables, listings, and graphs, as appropriate.

Study population

An overview on the number of subjects who were treated, withdrawn, and who completed the study is provided in Table S2.

Table S2 Number of subjects

	Overall	Placebo	MEDI7352 CCI	MEDI7352 CCI	MEDI7352 CCI
Planned[a]	272				
Screened	354				
Enrolled	112				
Randomised	112	54	6	16	36
Treated	107	54	4	14	35
Completed treatment	83	39	4	10	30
Completed study	86	40	4	12	30
Discontinued treatment	29	15	2	6	6
Discontinued study	26	14	2	4	6
Analysed (safety)	107	54	4	14	35
Analysed (modified intent-to-treat)	107	54	4	14	35
Analysed (pharmacokinetic)	107	54	4	14	35

a A planned MEDI7352 CCI dose group was not evaluated after the decision was made to terminate the study without completing Stage 4.

In terms of the disease under study (PDN) and concomitant diseases, age, body mass index, prior and concomitant medications the recruited population adequately represents the target population for the IP and is appropriate for the type of the study. The study protocol excluded females of childbearing potential, which may have resulted in a lower proportion of females represented in the recruited population (62.6% males versus 37.4% females). The study included almost exclusively subjects who were White and not Hispanic or Latino. However, PDN is also common in African-American and Hispanic populations. The concomitant medication use was considered reasonable in the clinical context. The subjects were almost equally assigned to receive placebo (54 subjects) or MEDI7352 (53 subjects). The demographics and baseline characteristics of the enrolled population were similar among the treatment groups or the observed small differences were not considered to have a potential influence on the results and their interpretation.

Summary of efficacy results

The primary objective was to assess the efficacy of MEDI7352 versus placebo on chronic pain in subjects with PDN currently taking standard of care medication for their PDN pain. This was evaluated by assessing the change in the weekly average of the average daily pain scores from the baseline week to Week 12 of MEDI7352 compared to placebo, as measured on an 11-point (0 to 10) NRS. The results showed that MEDI7352 at the dose of CCI is able to provide a statistically significant and clinically meaningful change from baseline in weekly average pain NRS at Week 12 compared with placebo (MEDI7352 CCI vs placebo: -1.39 [95% CI: -2.19 to -0.58], P=0.0009).

Secondary endpoints further demonstrated that:

- The weekly average daily pain score as measured on NRS gradually decreased in all groups with the largest and reliable impact observed in the MEDI7352 CCI group. Effect shown in the MEDI7352 CCI group is not considered reliable due to low sample size.
- Among all treatment groups the highest proportion of subjects with ≥30% or ≥50% improvement at Week 12 was seen in the MEDI7352 CCI group, in which 66.7% of subjects had a decrease of pain by ≥30% (P=0.0311 vs. placebo) and 42.4% had a decrease of pain by ≥50% (P=0.0029 vs. placebo). Thus, the statistical analysis indicates a significant association between the observed improvement from baseline and treatment.
- The total score for Galer neuropathic pain scale generally decreased from baseline and the decrease was more pronounced in the MEDI7352 groups, particularly with the CCI dose group. However, high interindividual variability was observed; for some subjects, across all treatment groups (except the MEDI7352 CCI group), an increase in the total score was observed during the study (worsening pain). Additionally, statistical analysis at Week 12 does not suggest a significant association between the treatment and observed CFB in any of the treatment groups.
- Daily sleep interference was gradually reduced (suggesting improved sleep) in all treatment groups including placebo. The biggest positive impact on sleep interference that can be considered reliable was seen in the MEDI7352 CCI group; statistical analysis for this group suggested a significant association between the observed effect and treatment at Week 12. The effect seen in the MEDI7352 CCI group is not considered reliable due to low sample size.
- The proportion of subjects who had ‘improved’, ‘much improved’ or ‘very much improved’ on the Patient Global Impression of Change (PGIC) increased slightly over time across all treatment groups, and the statistical analysis did not suggest an association between treatment and changes in the PGIC assessments.
- In general, the results of 36-Item Short-form Health Survey (SF-36) did not change during the study. Change from baseline data showed a slight improvement in the physical component score in all treatment groups; slight worsening in the mental component score was seen in all treatment groups except the MEDI7352 CCI group; change in general health (categorical data) was improved across all treatment groups, but particularly in the

MEDI7352 150 and [redacted] groups. However, no statistically significant differences between treatment groups were observed, except for the MEDI7352 [redacted] group, in which a slight improvement on mental health was estimated, although not considered reliable due to low sample size.

- Similar proportions of subjects took rescue medication in the placebo group (13.0%) and in the MEDI7352 [redacted] group (14.3%), with a slightly lower proportion for the MEDI7352 [redacted] group (8.6%). No subjects in the MEDI7352 [redacted] group took a rescue medication.

Summary of pharmacokinetic results

Relatively sparse PK samples were collected in this study for each subject, with only trough concentrations collected after the first 5 doses and more frequent sampling after the last dose administration on Day 70. Geometric mean MEDI7352 serum concentrations increased in a dose-dependent manner over the IV dose range investigated [redacted]. Based on Ctrough (pre-dose assessment) measurements, geometric mean concentrations decreased over time following repeat IV dose administration. Overall, data were highly variable.

The formation of ADAs appeared to impact the PK of MEDI7352. Across dose groups following repeat IV dose administration, in ADA negative subjects based on Ctrough (predose assessment) measurements, MEDI7352 concentrations were overall consistent over time, with no accumulation observed. By contrast, in ADA positive subjects, the PK profiles were highly variable in both the [redacted] IV dose groups. The PK profiles ranged from subjects showing overall similar profile to ADA negative subjects, to subjects with marked decrease in concentrations over time, following repeat IV dose administration.

Summary of pharmacodynamic results

Due to a change in the total NGF assay during the course of the study, only results in the MEDI7352 [redacted] and placebo groups are available. Geometric mean baseline total NGF serum concentration in the [redacted] IV dose group was 55.4 pg/mL versus 51.0 pg/mL in the placebo group. Following IV administration of MEDI7352 [redacted], geometric mean total NGF serum concentrations increased from baseline. Maximum geometric mean concentration was reached at Day 14. Thereafter concentration decreased from Day 14 to Day 28. From Day 28 to Day 56 pre-dose measurements remained approximately the same and further decreased on Day 70 to remain similar to Day 70 on Day 84. By contrast, in the placebo group geometric mean total NGF serum concentrations remained overall unchanged throughout the entire treatment period. Overall data were variable in the MEDI7352 [redacted] IV dose group.

The presence of ADAs appeared to impact the total NGF serum concentration-time profiles achieved following MEDI7352 administration. Following repeat IV dose administration of MEDI7352 [redacted], in ADA negative subjects total NGF serum trough concentration increased from baseline to reach a plateau after the first dose administered (i.e., Day 14)

which was sustained for the remainder of the treatment period. By contrast, in subjects who were ADA positive, overall, the total NGF serum concentrations were highly variable in the MEDI7352 [redacted] dose group. In general, ADA positive subjects did not maintain concentration levels achieved after the first dose administered, with concentrations in some subjects returning to around baseline levels.

Summary of pharmacogenetic results

There are no associated data to report in this CSR.

Summary of immunogenicity results

The overall ADA prevalence in the All MEDI7352 group was high (41/53, 77.4%), and was similar across the different dose cohorts (57.1% - 85.7%). The overall titer in the All MEDI7352 group was also high (median of maximum ADA titer 960). Most of the ADA positive subjects were classified as TE-ADA+ (40/53, 75.5%). ADAs appeared to affect both the PK and PD of MEDI7352, with MEDI7352 and total NGF serum concentrations being highly variable in ADA positive subjects. There was no apparent effect of ADAs on safety of MEDI7352, although the number of ADA negative subjects was low in the MEDI7352 treated group.

Summary of safety results

Treatment-emergent adverse events (TEAEs) were reported with higher incidence in subjects who received MEDI7352 (69.8%) when compared to subjects who received placebo (55.6%), with no specific trends identified in TEAEs reported to account for the imbalance. Most of the TEAEs were considered unrelated to the IP. Reported TEAEs were mostly mild and moderate; severe TEAEs were reported for 1 subject who received placebo (lung abscess) and 1 subject who received MEDI7352 (allodynia).

Serious adverse event was reported for 1 subject in the placebo group, who experienced serious severe lung abscess (not related to IP). No TEAE was life-threatening or fatal. Nine subjects (8.4%) discontinued IP due to a TEAE: 5 in the placebo group (9.3%) and 4 in the All MEDI7352 group (7.5%). Two subjects in the All MEDI7352 group developed 3 adverse events of special interest of infusion-related reaction, including 1 subject in whom this event led to discontinuation of treatment with the IP. There were no joint safety adverse events of special interest.

The most commonly reported TEAEs were reported under the “Infections and infestations” system organ class (SOC) and included events such as upper respiratory tract infection, urinary tract infection and nasopharyngitis. These events were reported in a smaller proportion of subjects who received MEDI7352. Other common TEAEs included events under the “Nervous system disorders” SOC, such as headache, which were reported with similar incidence between the placebo group and the All MEDI7352 group; however, paraesthesia

was reported with a greater incidence in the All MEDI7352 group than the placebo group (3.8% vs 0). Other common events included events under the "Gastrointestinal disorders" SOC, such as diarrhoea, which were more common in the placebo group. These events are common in the general population. Events reported with a ≥3.0% greater incidence in the All MEDI7352 group than in the placebo group were muscle spasms, alanine aminotransferase increased, blood glucose decreased, infusion related reaction, paraesthesia, and toothache.

No clinically relevant observations or trends were found in the clinical chemistry, haematology, coagulation, urinalysis, vital signs and electrocardiogram evaluations.

Results of physical and neurological exams, Total Neuropathy Score-Nurse, motor and sensory nerve conduction studies and strength and tendon reflexes were in concordance with usual findings in subjects with PDN. No relevant changes were observed in these parameters throughout the study.

Evaluation of hypersensitivity/anaphylactic reactions, injection-site reactions, and infusion-related reactions, drug-induced liver injury and infection risk, did not raise any concerns.

Overall, the safety profile of MEDI7352 was similar to that of placebo, with no unexpected safety findings.

Conclusions

- Administration of MEDI7352 at a dose of CCI every 2 weeks over a treatment period of 12 weeks provided clinically meaningful reduction of pain on NRS, which was statistically significantly different from placebo. At this dose, the majority of subjects had at least 30% of decrease of their pain.
- Improved sleep was observed, especially in the MEDI7352 CCI group. No meaningful difference was noted between MEDI7352 and placebo in the SF-36 quality of life questionnaire.
- Overall, the safety profile of MEDI7352 was similar to that of placebo, with no unexpected safety findings.
- ADA prevalence was high, with 75.5% of subjects having treatment-emergent ADAs. The presence of ADAs appeared to impact both the PK and PD of MEDI7352.