| **Clinical Study Report Synopsis** | |
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| Drug Substance | MEDI7352 |
| Study Code | D5680C00003 |
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# A Randomised, Double-blind, Placebo-controlled, Dose-response Study of the Efficacy and Safety of MEDI7352 in Subjects with Painful Osteoarthritis of the Knee

**Study Dates:**
First subject enrolled: 02 December 2020
Last subject last visit: 16 August 2023
The analyses presented in this report are based on a clinical data lock date of 14 September 2023

**Phase of Development:**
Therapeutic exploratory (IIb)

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

### Study centre(s)

Patients were enrolled and screened at 50 study sites across 7 countries.

### Publications

None at the time of writing this report.

### Objectives and criteria for evaluation

**Table S1 Objectives and Endpoints**

| Objectives | Estimand descriptions/Endpoints |
|---|---|
| Primary | |
| • To assess the efficacy of MEDI7352 compared with 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<br>• Primary endpoint:<br>° Change in weekly average of daily NRS pain scores from baseline to Week 12<br>• Intercurrent events:<br>° Discontinuation due to lack of efficacy or an AE<br>° Discontinuation due to other reasons such as loss to follow-up or external circumstances<br>° Taking prohibited pain medication during the treatment period<br>° Taking excessive permitted rescue medication<br>• Summary measures:<br>° Difference in mean changes in weekly average daily NRS pain scores between MEDI7352 doses and placebo<br>° 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 | |
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| • To assess the efficacy of MEDI7352 compared with placebo on additional measures of efficacy in participants with painful OA of the knee | Key secondary endpoints:<br>• Change in the WOMAC pain subscale from baseline to Week 12<br>• Change in the WOMAC physical function subscale from baseline to Week 12<br>• Change in the PGA of OA from baseline to Week 12<br>Other secondary endpoints:<br>• Change in the WOMAC pain subscale from baseline to Weeks 2, 4, 6, 8, 10, and 18<br>• Change in the WOMAC physical function subscale from baseline to Weeks 2, 4, 6, 8, 10, and 18<br>• Change in the WOMAC overall scores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 18<br>• Change in the WOMAC stiffness scores from baseline to Weeks 2, 4, 6, 8, 10, 12, and 18<br>• Change in PGA of OA from baseline to Weeks 2, 4, 8, 10, and 18<br>• Percentage of responders as measured by the OARSI responder index using the OMERACT-OARSI definition at Weeks 2, 4, 8, 12, and 18<br>• Percentage of participants who have achieved an improvement of ≥ 2 points in PGA of OA at Weeks 2, 4, 8, 12, and 18<br>• Change in the weekly average of daily NRS pain scores from baseline to Weeks 2, 4, 6, 8, 10, and 18<br>• 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<br>• Percentage of participants who have achieved ≥ 30% and ≥ 50%, reductions in WOMAC pain subscale scores at Weeks 2, 4, 8, 12, and 18.<br>• 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<br>• ADA titre |
| • To assess the safety and tolerability of MEDI7352 compared with placebo in participants with painful OA of the knee | • Safety and tolerability were be evaluated based on AEs, vital signs, and clinical laboratory assessments including but not limited to:<br>° AEs and SAEs<br>° Physical examinations<br>° Neurological examinations<br>° Total Neuropathy Score-nurse |

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| | ° Weight<br>° Vital signs (supine and standing BP, pulse rate, temperature, respiratory rate)<br>° Survey of Autonomic Symptoms<br>° 12-lead ECGs<br>° Clinical laboratory testing (haematology, chemistry, coagulation, and urinalysis)<br>° CRP (inflammatory biomarker)<br>° Concomitant medications and therapies<br>° Injection site reactions<br>° X-ray and/or MRI of large joints |

ADA, anti-drug antibody; AE(s), adverse event(s); BP, blood pressure; CRP, C-reactive protein; ECG, electrocardiogram; 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; SAE, serious adverse event; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.

## Study design

Study D5680C00003 was 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 osteoarthritis (OA), and not adequately controlled by standard-of-care treatments.

The study consisted 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 follow-up (FU) period (3 scheduled clinic visits and 4 phone calls).

After screening (Day -45 to Day -1), on Day 1 eligible participants were randomised in a 1:1:1:1:1 ratio to one of 5 treatment groups. Randomisation was performed using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM) system. Participants received investigational product (IP) by CCI injection once every 2 weeks (Q2W), for a total of 6 injections; the treatment groups were as follows:

- Group 1: MEDI7352 CCI injection (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Group 2: MEDI7352 CCI injection (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Group 3: MEDI7352 CCI injection (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Group 4: MEDI7352 CCI injection (Day 1 and Weeks 2, 4, 6, 8 and 10)
- Group 5: Placebo CCI injection (Day 1 and Weeks 2, 4, 6, 8 and 10)

At the end of the 12-week treatment period, or after the early termination (ET) visit for participants who discontinued IP, participants entered a 24-week FU period. The FU period

consisted of 3 clinic visits (Weeks 18, 32, and 36) and 4 FU phone calls (Weeks 15, 21, 24, and 28). Participants recorded daily pain scores (numerical rating scale [NRS]), daily sleep interference scale (DSIS) scores, and rescue medication from Day -14 until the FU visit at Week 18, and recorded Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire responses at different time points throughout the study. As of protocol amendment 2, safety X-ray imaging was performed on the knee and hip joints at the Week 32 visit, and the last study visit occurred at Week 36 to follow up on any new and clinically significant X-ray findings from the Week 32 visit. Prior to protocol amendment 2, the Week 32 visit occurred at Week 28, and the last study visit occurred at Week 32.

**Target population and sample size**

Eligible study participants were adults aged 18 to 80 years old with moderate-to-severe painful OA of the knee and a documented history of inadequate pain relief.

Approximately 350 eligible participants were to be randomly assigned to IP. Recruitment was to continue until statistical information equivalent to 255 evaluable participants was achieved or approximately 350 randomised participants, whichever was sooner. With statistical information equivalent to 255 evaluable participants, the study would 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.

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

MEDI7352 or placebo was administered CC [redacted] Q2W by study staff. MEDI7352 was provided by AstraZeneca; placebo was saline and was sourced locally by the study sites.

Three MEDI7352 batches were used in this study: CCI [redacted].

**Duration of treatment**

The duration of the treatment period was 12 weeks. Participants received their final dose of IP at Week 10.

**Statistical methods**

For the primary endpoint, change in weekly average daily NRS pain score, dose-response effects of MEDI7352 were evaluated using the MCP-Mod method, and pairwise statistical tests were used to evaluate each dose against placebo. The primary and key secondary endpoints were analysed following a hierarchical testing strategy.

For the primary analysis, the underlying model was an analysis of covariance (ANCOVA) with dependent variable ‘change from baseline to Week 12’, and independent variables

included dose, 'baseline score', and Kellgren and Lawrence (KL) grade at baseline. The random error was assumed to be normally and independently distributed with constant variance. To control the overall family-wise type 1 error at 2.5% (1-sided) across primary and key secondary endpoints for pairwise testing, the sequentially rejective multiple comparison approach was used (Bretz et al 2009). An attributable estimand strategy was adopted for missing or unevaluable data arising from any intercurrent events.

The key secondary efficacy variable of 'change in the WOMAC pain subscale from baseline to Week 12' was analysed using the same method as for the primary efficacy variable. The key secondary efficacy variables of 'change in the WOMAC physical function subscale from baseline to Week 12' and 'change in the Patient's Global Assessment (PGA) of OA from baseline to Week 12' were analysed using the same method as the primary efficacy variable but excluded the MCP-Mod test.

For other secondary endpoints, separate summary tables for observed cases only were produced. Continuous endpoints were analysed by ANCOVA and binary endpoints by logistic regression.

Pharmacokinetic (PK) concentration CCI [redacted] data were listed for each participant and each dosing day and timepoint, and descriptive summary statistics were provided by treatment group and timepoint for all evaluable participants and further subset by anti-drug antibody (ADA) status.

Immunogenicity variables were summarised descriptively. The number and percentage of participants who displayed detectable ADA within each ADA response category were summarised by treatment group and MEDI7352 Total.

CCI [redacted]

**Study population**

In total, 1228 participants were screened across 50 sites in 7 countries, of whom 345 were randomised to treatment groups: CCI [redacted] MEDI7352, CCI [redacted] CCI [redacted] to placebo. Of the randomised participants, 259 (75.1%) completed study treatment, and 85 (24.6%) discontinued treatment. One participant did not receive treatment.

Participant demographic and baseline characteristics were balanced across treatment groups. Participants had a mean (range) age of 63.7 years (43 to 81 years), and were predominantly White (96.8%) and female (66.7%). The mean body mass index across participants was 30.72 $kg/m^2$. Participant OA characteristics at baseline were similar across the treatment groups, with no notable differences in KL grades or pain intensity scores. The mean pain

intensity score was 6.93 and 25.2% had a KL grade of 2, 47.8% a grade of 3, and 27.0% a grade of 4.

**Summary of efficacy results**

The primary objective was not met. No statistically significant dose-response effect of MEDI7352 was observed (p = 0.029) in the change in weekly average of daily NRS pain scores from baseline to Week 12. As a consequence, all subsequent analyses were considered exploratory.

No statistically significant differences were seen in comparisons between MEDI7352 dose groups and placebo for the primary endpoint (difference estimate [95% confidence interval {CI}], CCI : -0.80 [-1.618, 0.009]; CCI -0.59 [-1.423, 0.245]).

Similarly to the primary endpoint, no differences were observed on changes from baseline to Week 12 for WOMAC pain or physical function subscales, or PGA of OA.

However, the analysis of the primary and key secondary endpoints may have been confounded by discontinuations due to coronavirus disease 2019 (COVID-19), which accounted for 25 of the 38 discontinuations due to adverse events (DAEs) during the study, and which were imputed as treatment failures for the purposes of the primary analysis. To investigate this post-hoc analyses were performed of the primary endpoint and the WOMAC pain subscale key secondary endpoint.

The post-hoc analysis found a statistically significant dose-response effect for MEDI7352 on the reduction of weekly average NRS pain scores (p = 0.011). The Emax model was selected for dose estimation (maximum response [Emax] = -1.036). The estimated dose at half of Emax (ED50) was CCI and the estimated maximally effective dose (asymptotic ED90) was CCI . The Emax estimated effect size (95% CI) for CCI MEDI7352 versus placebo was -0.923 (-1.604 to -0.242). No statistically significant effect was observed in the post-hoc analysis of WOMAC pain subscale scores.

The trends in the secondary endpoint analyses were consistent with a positive effect of MEDI7352:

- Average reductions in weekly average NRS pain scores, WOMAC pain and physical function subscales, and PGA of OA over time were consistently larger than those of placebo for the CCI MEDI7352 treatment groups.
- No dose-response relationships were observed with the multiple imputation analyses, however, apparent dose-response trends were visible in the observed cases analyses for NRS pain scores, WOMAC pain and physical function subscales, and PGA of OA.
- The proportions of participants who achieved ≥ 30% and ≥ 50% reductions in weekly average NRS pain score from baseline were higher in the MEDI7352 treatment groups

than placebo throughout the study period. Similar trends were seen for the higher MEDI7352 doses for WOMAC pain and physical function subscales, and PGA of OA scores.

- The proportion of Osteoarthritis Research Society International index responders tended to be higher than placebo for the CCI [redacted] MEDI7352 treatment groups.

**Summary of pharmacokinetic results**

Sparse PK samples were collected for each participant. Geometric mean (gmean) MEDI7352 serum concentrations increased in a dose-dependent manner over the dose range investigated. However, based on $C_{max}$ (7-day post-dose assessment) and $C_{trough}$ (pre-dose assessment) measurements, gmean concentrations decreased over time following repeat dose administration. Overall, the data were variable.

The PK of MEDI7352 appeared to be affected by ADAs. Across dose groups, in ADA negative participants, serum MEDI7352 $C_{max}$ (7-day post-dose assessment) and $C_{trough}$ (pre-dose assessment) measurements were consistent over time, with no accumulation observed following repeat doses. By contrast, in ADA positive participants, the PK profiles were highly variable across all MEDI7352 doses. The PK profiles ranged from participants showing overall similar $C_{max}$ and $C_{trough}$ to ADA negative participants, to participants with marked decrease in concentrations over time following repeat doses.

**Summary of pharmacodynamic results**

Geometric mean baseline total NGF serum concentrations ranged from 36.8 to 40.1 pg/mL across the MEDI7352 treatment groups, compared with 37.5 pg/mL in the placebo group. Following MEDI7352 administration, gmean total NGF serum concentrations increased from baseline at all doses. Maximum gmean concentration was reached at approximately Day 14. Thereafter, concentration decreased from Day 14 to Day 28. From Day 28 to Day 84, pre-dose measurements remained approximately the same in all MEDI7352 dose groups, except for the 25 mg group, which continued to decrease up to Day 56. In the placebo group, gmean total NGF serum concentrations remained overall unchanged throughout the treatment period. Overall, the data were variable.

The pharmacodynamics (PD) of MEDI7352 appeared to be affected by ADAs. In ADA negative participants across dose groups, total NGF serum concentration increased from baseline to reach a plateau after the first dose administered, which was sustained for the remainder of the treatment period. In contrast, total NGF serum concentrations were highly variable in ADA positive participants. Total NGF profiles ranged from sustained concentrations similar to those observed in ADA negative participants, to concentrations returning towards baseline levels post Day 14.

**Summary of immunogenicity results**

The ADA prevalence in MEDI7352-treated participants was 83.4% (226/271 participants) and the ADA incidence was 81.2% (220/271), with 57.9% (157/271) of participants persistently positive. At baseline, ADA prevalence was 11.4% (31/271), and increased to 59.3% (156/263) at Week 2. This increased further to 66.7% (158/237) of participants at Week 4, after which it was fairly consistent for the remainder of the study. ADA responses were similar across all MEDI7352 treatment groups.

The median (range) ADA titre in MEDI7352-treated participants was high at 960 (30 – 245760), noting that lowest reportable titre in this assay was 30. ADA titres reached a maximum at Week 2, remained steady and tapered off to the level observed in the placebo group at Week 28 and Week 32, the last 2 sampling time points of the study.

There was no apparent effect of ADA status on efficacy or safety, however the number of ADA negative participants was too low to allow robust comparison to be made. In contrast, the PK and PD (total NGF) of MEDI7352 appeared to be affected by ADAs.

**Summary of safety results**

In total, 275 participants received MEDI7352, of whom 197 (71.6%) completed all 6 doses, and 69 participants received placebo, of whom 48 (69.6%) completed all 6 doses. The mean duration of exposure was 10.65 weeks in MEDI7352-treated participants and 10.62 weeks in placebo.

Overall, 73.1% (201/275) of MEDI7352-treated participants experienced a treatment-emergent adverse event (TEAE), compared with 59.4% (41/69) of placebo-treated participants. The incidence of TEAEs was broadly similar across the MEDI7352 treatment groups. The TEAEs that occurred with ≥ 3% higher frequency than placebo in MEDI7352-treated participants overall were COVID-19, headache, injection site erythema, paraesthesia, urinary tract infection, diarrhoea, and injection site reaction. The TEAEs that occurred with ≥ 3% higher frequency in the placebo group were lower respiratory tract infection, nasopharyngitis, pain in extremity, and injection site bruising.

Serious adverse events (SAE) were reported by 4.4% (12/275) of MEDI7352-treated participants and 2.9% (2/69) of placebo-treated participants. No SAE by preferred term occurred in more than one participant, and there were no deaths during the study.

The incidence of adverse events of special interest (AESIs) was 1.8% of MEDI7352-treated participants and 4.3% of placebo-treated participants. In the MEDI7352 treatment groups there was one instance each of: Henoch-Schonlein purpura, rapidly progressive osteoarthritis (RPOA) type 1, subchondral insufficiency fracture (SIF), injection site erythema, and

injection site reaction. In the placebo group there was one AESI of COVID-19 and 2 of RPOA type 1.

In total, 32 (11.6%) MEDI7352-treated participants and 6 (8.7%) placebo participants experienced a DAE. The majority of DAEs were due to COVID-19, reported for 21 (7.6%) MEDI7352-treated participants and 4 (5.8%) placebo participants.

**Conclusion(s)**

- The primary endpoint was not met: no statistically significant effect was observed for MEDI7352 on the change in weekly average of daily NRS pain scores at Week 12 ($p = 0.029$).
- The primary endpoint result may have been influenced by the incidence of COVID-19 infection in the MEDI7352 treatment groups, which required IP discontinuation per the protocol. In a post-hoc analysis in which COVID-19 discontinuations were not imputed as treatment failures, there was a statistically significant reduction in weekly average NRS pain scores ($p = 0.011$; Emax estimated effect size for CCI MEDI7352 versus placebo = -0.923).
- Dose-response trends in efficacy data for weekly average NRS pain score, WOMAC pain, physical function, and PGA of OA over time were consistent with an improvement in MEDI7352-treated participants, particularly at the CCI dose level.
- The majority of MEDI7352-treated participants developed ADAs by Week 2. The presence of ADAs appeared to impact both the PK and PD of MEDI7352. There was no apparent effect of ADA status on efficacy or safety, however the number of ADA negative participants was too low to allow for robust comparison to be made.
- Overall, the safety profile of MEDI7352 was similar to placebo, with no unexpected findings.