Synopsis – Trial 20007A

Trial Title Interventional, randomized, double-blind, parallel-group, placebo-controlled study of add-on eptinezumab treatment to brief educational intervention for the preventive treatment of migraine in patients with dual diagnosis of migraine and medication overuse headache
Investigators 76 principal investigators at 76 sites in 11 countries *Signatory investigator* – [redacted]
Trial Sites 76 sites – 5 in Australia, 2 in Denmark, 11 in France, 8 in Germany, 7 in Georgia, 14 in Italy, 1 in Netherlands, 4 in Norway, 14 in Spain, 4 in Sweden, and 6 in United States
Publications Jensen RH, Schytz HW, Tassorelli C, Terwindt GM, Carlsen LN, Mittoux A, et al. Adding eptinezumab to brief patient education to treat chronic migraine and medication-overuse headache: Protocol for RESOLUTION-A phase 4, multinational, randomized, double-blind, placebo-controlled study. Front Neurol. Feb 2023; 14: 1114654.
Trial Period *First participant first visit* – 1 July 2022 (the date when the first *Informed Consent Form* was signed) *Last participant last visit* – 13 March 2025 (the date of the last protocol-specified contact with any participant)
Report Date 07 August 2025
This trial was conducted in compliance with *Good Clinical Practice*.

Objectives, and Endpoints, and Estimands

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH	**Primary Endpoint:** – change from Baseline in the number of MMDs (Weeks 1-4) **Key Secondary Endpoints:** – change from Baseline in MMDs (Weeks 1-12) – change from Baseline in the number of MHDs (Weeks 1-4) – Change from Baseline in MHDs (Weeks 1-12) – not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4) – not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-12) – change from Baseline in average Daily Pain assessment score (Weeks 1-2) – change from Baseline in MAMDs (Weeks 1-4) – change from Baseline in MAMDs (Weeks 1-12)

Objectives	Endpoints
	Secondary Endpoints: – not fulfilling the ICHD-3 diagnostic criteria for CM (Weeks 1-4, Weeks 1-12) – not fulfilling the ICHD-3 diagnostic criteria for MOH (Weeks 1-4, Weeks 1-12) – change from Baseline in MMDs with use of acute headache medication (Weeks 1-12) – change from Baseline in monthly days with triptan or ergotamine medication use (Weeks 1-12) – change from Baseline in monthly days with individual non-opioid analgesics or NSAID medication use (Weeks 1-12) – change from Baseline in monthly days with combination non-opioid analgesics medication use (Weeks 1-12) – migraine on the day after dosing (Day 1) – response: ≥50% reduction from Baseline in MMDs (Weeks 1-4, Weeks 1-12) – response: ≥75% reduction from Baseline in MMDs (Weeks 1-4, Weeks 1-12) – response: ≥50% reduction from Baseline in MHDs (Weeks 1-4, Weeks 1-12) – response: ≥75% reduction from Baseline in MHDs (Weeks 1-4, Weeks 1-12) – change from Baseline in rate of migraines with severe pain intensity (Weeks 1-4, Weeks 1-12) – change from Baseline in rate of headaches with severe pain intensity (Weeks 1-4, Weeks 1-12) – PGIC score at Week 4 and Week 12 – MBS score at Week 12 **Exploratory Endpoints:** – complete withdrawal of acute headache medication (Weeks 1-4, Weeks 5-8, Weeks 9-12) – change from Baseline in number of days with auras without headache (Weeks 1-4, Weeks 1-12) – change from Baseline in number of days with severe pain (Weeks 1-4, Weeks 1-12)
Primary Estimand Key elements to the primary estimand: the analyses of the primary endpoint aimed to estimate "the treatment effect that was seen in the population, regardless of the use of preventive migraine medication, assuming other anti-CGRP treatment was not available." Complete set of attributes of the primary estimand: • Intercurrent events and strategies – initiation of a new preventive migraine medication other than anti-CGRP treatment, during the trial period (Strategy: Treatment policy)	

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">

use of disallowed anti-CGRP medication other than eptinezumab as preventive migraine medication (Strategy: Hypothetical)
interruption/termination of infusions (Strategy: Treatment policy)

Treatment condition of interest
the treatment condition of interest was eptinezumab 100 mg compared to placebo provided as add-on to the BI.
Population
the population was the entire trial population, that was, participants who suffered from migraine and MOH and who fulfilled the inclusion and exclusion criteria.
Variable
change from Baseline in MMDs (Weeks 1-4)
Population-level summary
the population-level summary for the primary endpoint was the mean difference in the change from Baseline in MMDs (Weeks 1-4) between participants on eptinezumab and placebo.

</td></tr>
<tr><td colspan="2">Key Secondary Estimands

For continuous key secondary endpoints, estimands followed the same rationale and strategies as for the primary endpoint to address intercurrent events. For the binary key secondary endpoints Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4, Weeks 1-12), the estimand was ‘odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between eptinezumab 100 mg with BI and placebo with BI regardless of the use of preventive migraine medication and interruptions/terminations of infusions, assuming other anti-CGRP treatment was not available’ with the variable being the only attribute differing from the primary estimand attributes. The variables for these binary key secondary endpoints were ‘odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo across Weeks 1-4’, and ‘Odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo across Weeks 1-12’, respectively.</td></tr>
<tr><td>Secondary Objectives

To evaluate the efficacy of eptinezumab as add-on to BI on health-related quality of life and work productivity</td><td>Secondary endpoints

change from Baseline to Week 4, and from Baseline to Week 12 in the HIT-6 total score
change from Baseline to Week 4 and from Baseline to Week 12 in the mMIDAS total score
change from Baseline to Week 4, and from Baseline to Week 12 in the MSQ v2.1 sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function)
change from Baseline to Week 4, and from Baseline to Week 12 in the EQ-5D-5L VAS score
migraine specific HCRU at Baseline and at Week 12
change from Baseline to Week 12 in the WPAI:M sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment)
change from Baseline to Week 4, and from Baseline to Week 12 in HADS-depression, and anxiety subscale scores
TSQM-9 score at Week 4 and Week 12</td></tr>
</table>

Objectives	Endpoints
• To evaluate the efficacy of eptinezumab during the 12-Week open-label extension period	– change from Baseline to Week 24 in the HIT-6 total score – change from Baseline to Week 24 in the mMIDAS total score – change from Baseline to Week 24 in the MSQ v2.1 sub-scores – change from Baseline to Week 24 in the EQ-5D-5L VAS score – migraine specific HCRU at Week 24 – change from Baseline to Week 24 in the WPAI:M sub-scores – change from Baseline to Week 24 in HADS - depression and anxiety subscale scores – PGIC score at Week 24 – MBS score at Week 24 – TSQM-9 score at Week 24 – change from Baseline in MMDs (Weeks 13-24) – change from Baseline in MHDs (Weeks 13-24) – not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 13-24) – change from Baseline in MAMDs (Weeks 13-24) – change from Baseline in average Daily Pain assessment score (Weeks 13-24) – change from Baseline in monthly days with triptan or ergotamine medication use (Weeks 13-24) – change from Baseline in monthly days with individual non-opioid analgesics or NSAID medication use (Weeks 13-24) **Exploratory Endpoints** – change from Baseline in number of days with aura without headache (Weeks 13-24) – change from Baseline in number of days with severe pain (Weeks 13-24)

Objectives	Endpoints
Exploratory Objectives • To investigate the efficacy of eptinezumab as add-on to BI on level of daily physical activity and sleep using a wearable digital device (subset)	**Exploratory Endpoints** • Change from Baseline in passive registration of movement (actigraphy) (Weeks 1-4 and Weeks 1-12, average per 28 days) – minutes in no motion (0 - <10 a.U.) – minutes with light motion (10- <50 a.U.) – minutes with moderate motion (50- <100 a.U.) – minutes with vigorous motion (≥100 a.U.) • Change from Baseline to Week 4 and Week 12 in sleep metrics assessment as assessed by actigraphy (average per 28 days) – total Sleep Time (minutes per night) – sleep Efficiency (percentage per night) – wake After Sleep Onset (minutes per night) – sleep Onset Latency (minutes per night) All analyses were also done by week, for example change from Baseline to Week 1, Baseline to Week 2, and Baseline to Week 12.
• To investigate efficacy of eptinezumab as add-on to BI on the level of analgesic dependence	– change from Baseline to Week 12 in SDS:H score
Safety Objective • To evaluate the safety and tolerability of eptinezumab	**Safety Endpoints** – adverse events – absolute values and changes from Baseline in vital signs – potentially clinically significant vital signs changes
BI = brief educational intervention; CGRP = calcitonin gene-related peptide; CM = chronic migraine; EQ-5D-5L VAS = Euroqol 5 Dimension – 5 Levels Visual Analogue Scale; HADS = Hospital Anxiety and Depression Scale; HCRU = Health Care Resources Utilization; HIT-6 = Headache Impact Test; ICHD-3 = International Classification of Headache Disorders; MAMD = monthly days with acute headache medication use; MBS = most bothersome symptom; MHD = monthly headache day; MOH = medication overuse headache; MMD = monthly migraine day; mMIDAS = modified Migraine Disability Assessment; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire; NSAID = non-steroidal anti-inflammatory drug; PGIC = Patient Global Impression of Change; SDS:H = Severity Dependence Scale adapted for headache; TSQM-9 = Treatment Satisfaction Questionnaire for Medicine – 9 items; WPAI:M = Work Productivity and Activity Impairment Questionnaire, Migraine version	

Trial Methodology

This was a multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled trial designed to demonstrate the efficacy and safety of add-on treatment with eptinezumab to brief educational intervention (BI) conducted at Baseline, for the prevention of migraine and treatment of medication overuse headache (MOH) in participants with a dual diagnosis of chronic migraine (CM) and MOH.

The 12-week Placebo-controlled Period was followed by a 12-week Open-label Period, during which all participants received eptinezumab 100 mg. The Open-label Period aimed to provide treatment to participants who had received placebo during the Placebo-controlled Period and, to offer continued relief and maintenance of CM and MOH remission for those who received eptinezumab 100 mg during the Placebo-controlled Period. Safety and tolerability were assessed throughout the trial.

The trial consisted of:

- Screening Period – 28-day period from screening to randomization
- Placebo-controlled Period – 12-week double-blind treatment period with placebo or eptinezumab 100 mg as add-on to BI
- Open-label Period – 12-week open-label treatment with eptinezumab 100 mg
- Safety Follow-up Period – 8-week period after completion of the trial or after withdrawal from the trial

Eligible participants were, after receiving BI, randomly allocated, via a centralised randomization system, to receive eptinezumab 100 mg or placebo, in a ratio of 1:1. Randomization was stratified by country and number of previous preventive treatment failures (≤2; >2) by using the interactive response technology system.

Participants were instructed at the Baseline Visit to stop or reduce the use of acute headache medications to levels below medication overuse during a semi-structured brief educational intervention (that is, BI). The BI started with 5 questions from the scale Severity Dependence Scale adapted for headache (SDS:H) (including an indication of the participant's willingness and confidence to change his/her medication overuse). Then, the participants were shown a short-structured scheme-based presentation with information about MOH and the association between medication overuse and recurrent headaches. The interview ended with an agreed plan on how to stop the medication overuse.

Participants received BI and investigational medicinal product (IMP) (eptinezumab or placebo) at Baseline Visit during the Placebo-controlled Period and IMP (eptinezumab) at Week 12 Visit during the Open-label Period. IMP was administered by IV infusion over 30 minutes (with possibility to extend the IV infusion by 15 minutes). The End of Trial Visit was conducted at Week 24, 12 weeks after the second IMP infusion. Participants were scheduled for a Safety Follow-up Contact (at Week 32), 8 weeks after End-of-Trial Visit (or 20 weeks after the last IMP infusion).

At designated participating countries, optional actigraphy assessments using a digital device were conducted on a consenting subset of participants. Participants could withdraw from these optional assessments without withdrawing from the trial.

Number of Participants Planned

570 participants were planned for randomization: 285 to the placebo group and 285 to the eptinezumab group.

Diagnosis and Main Selection Criteria

The participants had to be outpatients with a primary diagnosis of CM and MOH according to International Headache Society International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria, confirmed at Screening Visit. For each month within the past 3 months prior to the Screening Visit the participant had:

- ≥15 headache days, of which ≥8 days were assessed as migraine days migraine days
- regular overuse of one or more drugs that can be taken for acute treatment of headache

and who:

- were ≥18 and ≤75 years of age with an onset of migraine diagnosis at ≤50 years of age
- had a history of migraine onset at least 12 months prior to the Screening Visit
- had ≥15 headache days, of which ≥8 days were assessed as migraine days during the Screening Period, based on prospectively collected information in the electronic diary (eDiary)
- had overused drugs that could be taken for acute treatment of headache during the Screening Period, based on prospectively collected information in the eDiary
- had a history of treatment failure with at least 1 preventive treatment within the last 5 years prior to the Screening Visit. Participants were excluded if they had a history of treatment failure with a previous treatment targeting the calcitonin gene-related peptide (CGRP) pathway for acute or preventive use within the last 5 years prior to the Screening Visit

Key exclusion criteria included history or diagnosis of any other type of headache or migraine (including new daily persistent headache); confounding and clinically significant pain syndromes; any psychiatric conditions with symptoms not controlled; and any history of clinically significant cardiovascular disease.

Investigational Medicinal Product (IMP), Dose, and Mode of Administration

Active

Eptinezumab – 100 mg; concentrate for solution for infusion, 100 mg/mL added to 100 mL of 0.9% saline solution (prepared on site), IV

Control

Placebo: for blinding – 100 mL of 0.9% saline solution (prepared on site), IV

Duration of Treatment

Placebo-controlled Period: 12 weeks; Open-label Period: 12 weeks

Statistical Methodology

The following analysis sets were used to analyse and present the data:

- *all-patients-screened set* (APSS) – all screened participants
- *all-patients-randomized set* (APRS) – all randomized participants
- *all-patients-treated set* (APTS) – all participants in the APRS who received an infusion of the IMP in the Placebo-controlled Period
- *full-analysis set* (FAS) – all participants in the APTS who had a valid Baseline assessment and at least one valid post-Baseline 4-week assessment of monthly migraine days (MMDs) in Weeks 1-12
- *all-patients-treated-open-label set* (APTS-OL) – all participants in the APRS who received an infusion of the IMP in the Open-label Period
- *all-patients-treated-follow-up set* (APTS-FU) - all participants in the APTS who are not in the APTS-OL, and who have data collected from the Safety Follow-up Visit.

Unless otherwise specified, the FAS and APTS was used for all efficacy analyses and safety analyses, respectively, in the Placebo-controlled Period. The APTS-OL was used for both safety and efficacy analyses in the Open-label Period. Relevant safety outputs for data collected at the Safety Follow-up Visit were listed for the APTS-FU.

Primary Endpoint

Change from Baseline in MMDs (Weeks 1-4) was analysed using mixed model for repeated measures (MMRM) as described below.

Changes from Baseline in the number of MMDs at the 4-Week intervals (Weeks 1-4, Weeks 5-8, Weeks 9-12) was analysed using a restricted maximum likelihood-based MMRM approach. The model included the following fixed effects: Baseline number of MMDs as a continuous covariate, treatment group (eptinezumab 100 mg with BI *versus* placebo with BI), month (Month 1: Weeks 1-4; Month 2: Weeks 5-8; Month 3: Weeks 9-12), country, and previous treatment failures (≤2; >2) as factors. The interaction terms treatment-by-month and previous treatment failures (≤2; >2) by month as well as number of MMDs at Baseline-by-month were included. An unstructured covariance matrix was used to model the between and within-participant covariance. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

The primary estimand was the mean difference in change from Baseline in MMDs (Weeks 1-4) in participants with a dual diagnosis of CM and MOH treated with add-on eptinezumab 100 mg to BI and add-on placebo to BI, regardless of use of preventive migraine treatment, assuming other anti-CGRP treatment was not available and regardless of infusion interruption or termination before full dose was received.

The mean differences between eptinezumab 100 mg with BI and placebo with BI estimates were presented with p-values and 95% CIs. The primary comparison was the contrast between eptinezumab 100 mg with BI and placebo with BI at Weeks 1-4. If the two-sided

p-value for this comparison was <0.05 and favoured eptinezumab, the primary analysis had shown statistical significance favouring eptinezumab 100 mg with BI over placebo with BI.

Sensitivity, subgroup, and exploratory analyses for the primary endpoint were conducted.

Key Secondary Endpoints

Change from Baseline in MMDs (Weeks 1-12) was estimated using MMRM as described for the primary analysis, except that the test was based on the estimated mean MMDs, averaged over Weeks 1-4 (Month 1), Weeks 5-8 (Month 2), and Weeks 9-12 (Month 3).

Change from Baseline in monthly headache days (MHDs) (Weeks 1-4 and Weeks 1-12) were estimated using the same methodology as for the primary analysis, except that the model analysed the number of MHDs. The Baseline MMDs were replaced with Baseline MHDs.

Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4 and Weeks 1-12) was analysed using logistic regression with Baseline MMDs as a covariate, and treatment group, country, and previous treatment failures (≤2, >2) as categorical variables.

Daily Pain assessment score (Weeks 1-2) was analysed using an analysis of covariance with the average Daily Pain at Baseline as a covariate and including treatment group, country, and previous treatment failures, as categorical variables.

Change from Baseline in monthly days with acute headache medication use (MAMDs) (Weeks 1-4 and Weeks 1-12) were estimated using the same methodology as utilised for the primary analysis, except that the model analysed MAMDs. The Baseline MMDs were replaced with MAMDs at Baseline.

For continuous key secondary endpoints, estimands followed the same rationale and strategies as for the primary endpoint to address intercurrent events. For the binary key secondary endpoints "not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4 and Weeks 1-12)", the estimand was 'odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between eptinezumab 100 mg with BI and placebo with BI regardless of the use of preventive migraine medication and interruptions/terminations of infusions, assuming other anti-CGRP treatment was not available' with the variable being the only attribute differing from the primary estimand attributes. The variables for these binary key secondary endpoints were 'odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo across Weeks 1-4', and 'odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo across Weeks 1-12', respectively.

Sensitivity and exploratory analyses for the key secondary endpoints were conducted.

Testing Strategy

For the primary endpoint (change from Baseline in MMDs [Weeks 1-4]), test the hypothesis of no difference between the eptinezumab and placebo groups using a two-sided test on 5% significance level. If rejected and if the test showed a numerical advantage to eptinezumab, then it was planned to continue to the first key secondary endpoint (change from Baseline in MMDs [Weeks 1-12]).

On the first key secondary endpoint, test the hypothesis of no difference between the eptinezumab and placebo groups. If rejected and if the test showed a numerical advantage to eptinezumab, then continue to the second key secondary endpoint (change from Baseline in MHDs [Weeks 1-4]). This continued through the list of key secondary endpoints (change from Baseline in MHDs [Weeks 1-12], not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH [Weeks 1-4], not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH [Weeks 1-12], change from Baseline in average Daily Pain assessment score [Weeks 1-2], change from Baseline in MAMDs [Weeks 1-4], change from Baseline in MAMDs [Weeks 1-12]), until an endpoint failed to reach significance.

Sample Size Considerations

It was assumed that the treatment effect of eptinezumab 100 mg compared to placebo in change from Baseline in MMDs (Weeks 1-4) was -1.5 MMDs. Furthermore, the SD for the change from Baseline in MMDs (Weeks 1-4) was assumed to be 6.2.

Based on the assumed effect size and SD, using a two-sided test on the 5% significance level, 270 participants per treatment group provided 80% power for showing an effect on the primary endpoint. Assuming 5% of participants could not contribute data to the analysis, 285 participants were randomized per treatment group (570 participants in total).

Sample size re-assessment was conducted on blinded data when approximately 70% of the participants had been randomized. This led to no change of the sample size.

Participant Disposition and Analysis Sets

Placebo-controlled Period

Participant disposition for the Placebo-controlled Period is summarised below.

Participant Disposition During Placebo-Controlled Period (APRS)

	BI + EPTI (N = 305) n (%)	BI + PBO (N = 303) n (%)	Total (N = 608) n (%)
Number of treated participants during the period	303 (99.3)	301 (99.3)	604 (99.3)
Number of participants who completed the period	301 (98.7)	295 (97.4)	596 (98.0)
Number of participants who withdrew from trial during the period	2 (0.7)	6 (2.0)	8 (1.3)
Primary reason for withdrawal from trial			
Withdrawal of consent	0	4 (1.3)	4 (0.7)
Lost to follow-up	1 (0.3)	0	1 (0.2)
Failure to comply with trial procedures	0	1 (0.3)	1 (0.2)
Other	1 (0.3)	1 (0.3)	2 (0.3)
All reasons for withdrawal from trial[a]			
Withdrawal of consent	0	5 (1.7)	5 (0.8)
Lost to follow-up	1 (0.3)	0	1 (0.2)
Failure to comply with trial procedures	0	4 (1.3)	4 (0.7)
Other	1 (0.3)	3 (1.0)	4 (0.7)

APRS = all-patients-randomized set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; PBO = placebo

Note: Percentages were based on the number of participants in the APRS.

a Participants could have had more than one reason for withdrawal from trial, and each participant contributed only once for each reason.

Open-label Period

Participant disposition for the Open-label Period is summarised below.

Participant Disposition During the Open-label Period by Treatment Sequence (APTS-OL)

	BI + EPTI-EPTI (N = 300) n (%)	BI + PBO-EPTI (N = 293) n (%)	Total (N = 593) n (%)
Number of treated participants during the period	300 (100)	293 (100)	593 (100)
Number of participants who completed the period	294 (98.0)	290 (99.0)	584 (98.5)
Number of participants who withdrew from trial during the period	6 (2.0)	3 (1.0)	9 (1.5)
Primary reason for withdrawal from trial			
Withdrawal of consent	2 (0.7)	1 (0.3)	3 (0.5)
Lost to follow-up	3 (1.0)	0	3 (0.5)
Failure to comply with trial procedures	0	0	0
Other	1 (0.3)	2 (0.7)	3 (0.5)
All reasons for withdrawal from trial[a]			
Withdrawal of consent	3 (1.0)	1 (0.3)	4 (0.7)
Lost to follow-up	3 (1.0)	0	3 (0.5)
Failure to comply with trial procedures	3 (1.0)	1 (0.3)	4 (0.7)
Other	1 (0.3)	2 (0.7)	3 (0.5)

APTS-OL = all-patients-treated-open-label set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; PBO = placebo

Note: Percentages were based on the number of participants in the APTS-OL.

a Participants may have more than one reason for withdrawal from trial and each participant contributed only once for each reason.

Analysis Sets (APSS)

	BI + EPTI n (%)	BI + PBO n (%)	Total n (%)
Number of participants screened			928
Number of screen failures			320
All-Participants-Randomized Set	305	303	608
All-Participants-Treated Set	303 (99.3)	301 (99.3)	604 (99.3)
Full-Analysis Set	302 (99.0)	300 (99.0)	602 (99.0)
All-Participants-Treated-Open-Label Set	300 (98.4)	293 (96.7)	593 (97.5)
All-Participants-Treated-Follow-Up Set	2 (0.7)	6 (2.0)	8 (1.3)

APSS =all-patients-screened set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; PBO = placebo.

Note: Percentages were based on the number of participants in the All-Participants-Randomized Set.

Demographics and Baseline Characteristics of the Trial Population

The two groups were comparable with respect to demographics: the mean age of participants was 45.5 years (range: 18 to 72 years). The majority of the participants were women (86%). Participants were mainly enrolled at sites in Europe (98%). Overall, the mean body mass index of participants was 25.4 kg/m^2 (range: 15.8 to 39.0 kg/m^2).

The trial participants documented a long disease duration of a dual diagnosis of CM and MOH, with MOH being diagnosed in adulthood. The two groups were generally similar in migraine characteristics at Baseline. Overall, mean age at migraine onset was 25.6 years (range: 3 years to 66 years). The mean time since the first migraine diagnosis prior to Baseline was 20.4 years.

The mean time since first MOH diagnosis was 5.0 years, and the mean age at first MOH diagnosis was 41.0 years.

The majority (56.0%) of participants had ≤2 previous preventive treatment failures as recorded in the interactive response technology system. The most common reasons for treatment failure were lack of efficacy (88.1%) and safety/tolerability issues (52.5%). The most common (>25%) medications leading to treatment failure were amitriptyline (49.2%), topiramate (39.9%), and propranolol (25.2%).

In general, Baseline characteristics were consistent between the treatment groups in terms of eDiary-reported migraine characteristics and electronic patient-reported outcome (ePROs) for efficacy assessments.

At Baseline, participants reported a mean of 20.9 migraine days, 21.7 headache days, 20.1 acute headache medication days, and 18.6 migraine attacks per month. Participants also

reported a mean of 43.8% migraine attacks with severe pain intensity, which indicated a high migraine disease burden.

The most common (>10% of overall participants) most bothersome symptom (MBS) included pain with activity (20.8%), sensitivity to light (20.4%), fatigue (15.6%), nausea (12.3%), and sensitivity to sound (10.3%).

The mean SDS:H score was 8.6, which is a consistent with a significant level of medication dependence; cut-off score for diagnosing behavioural addiction for painkillers being ≥5.

Hospital Anxiety and Depression Scale (HADS)-depression and HADS-anxiety mean scores were 6.3, and 7.1, respectively. These mean values were approximately between the cut-off score for *absence and doubtful* symptomatology of depression and anxiety.

The mean Headache Impact Test (HIT)-6 score was 66.5, indicating a severe impact of headache on daily functioning.

The mean modified Migraine Disability Assessment (mMIDAS) total score for 1-month period was 31.5. The total mMIDAS score multiplied by 3 was 94.6 for converting to MIDAS score on 3-month period. These mMIDAS and MIDAS scores indicate severe disability and reduced participation in daily activities.

The mean Migraine-Specific Quality of Life Questionnaire (MSQ) v2.1 role function restrictive, role function preventive, and emotional function scores were 34.7, 51.8, and 42.3, respectively, indicating a poor quality of life.

The mean Euroqol 5 Dimension – 5 Levels Visual Analogue Scale (EQ-5D-5L VAS) score was 66.3, indicating a negative impact of migraine on overall well-being.

The mean Work Productivity and Activity Impairment Questionnaire, Migraine version (WPAI:M) work productivity loss score and activity impairment score were 60.8 and 62.4, respectively.

The Baseline characteristics were similar between the two groups also in terms of migraine specific healthcare resources utilization (HCRU).

Altogether, the data confirmed the high levels of drug dependency, psychological and disease related burden, and daily functioning impairment of the participants, well-representative of participants with a dual diagnosis of CM and MOH.

There were no clinically relevant differences in the past or concurrent medical, psychiatric, or neurological disorders between the treatment groups.

Exposure

Placebo-controlled Period

The majority of participants completed the treatment as planned during the Placebo-controlled Period in both the eptinezumab and placebo groups. Completion rates for the two groups were 100% and 99.7% for the IMP infusion, respectively.

Open-label Period

The majority of participants completed the treatment as planned during the Open-label Period in both the eptinezumab 100 mg – eptinezumab 100 mg (EPTI-EPTI) and placebo – eptinezumab 100 mg (PBO–EPTI) treatment sequence groups. Completion rates for the two treatment sequence groups were 100% and 97.3% for the IMP infusion, respectively.

Efficacy Results

Placebo-controlled Period

Statistically significant treatment effects ($p < 0.0001$) favouring eptinezumab 100 mg as add-on to BI *versus* placebo as add-on to BI were seen for the primary and all key secondary efficacy endpoints included in the sequential testing hierarchy.

In this trial, the primary endpoint (MMRM, FAS) was achieved and eptinezumab 100 mg as an add-on to BI demonstrated statistically significant reduction in the number of MMDs *versus* placebo as add-on to BI during Weeks 1-4. The LS mean change from Baseline in the number of MMDs (Weeks 1-4) for the eptinezumab and for placebo groups was -6.85 days and -3.66 days, respectively. The difference between eptinezumab and placebo was -3.20 days (95% CI: -4.16, -2.23) and was statistically significant ($p < 0.0001$). The results of the sensitivity analyses, subgroup analyses, and exploratory analyses of the primary endpoint were consistent with the results of the primary analysis.

Analysis of Change from Baseline in Number of MMDs Weeks 1-4, Primary Endpoint Using MMRM (FAS)

	BI + EPTI (N = 302)	BI + PBO (N = 300)
Baseline		
n	302	300
Mean (SD)	21.00 (4.261)	20.85 (4.279)
Median	21.00	20.46
Min, Max	10.8, 28.0	8.2, 28.0
Weeks 1-4		
n	300	299
Mean (SD)	13.59 (7.648)	16.67 (6.746)
Median	12.88	16.15
Min, Max	0.0, 28.0	0.0, 28.0
Change from Baseline at Weeks 1-4		
n	300	299
Mean (SD)	-7.41 (6.648)	-4.20 (5.716)
Median	-7.26	-3.68
Min, Max	-27.0, 10.0	-27.0, 11.0
Least-squares Mean (SE)	-6.85 (0.518)	-3.66 (0.519)
Difference from BI + Placebo (SE)	-3.20 (0.490)	
95% CI	(-4.16, -2.23)	
P-value	<0.0001	

BI = brief educational intervention; EPTI = eptinezumab 100 mg, FAS = full-analysis set; MMD = monthly migraine day; MMRM = mixed model for repeated measures; PBO = placebo

Note: The MMRM model included fixed effects: Baseline number of MMDs as a continuous covariate, treatment group (BI + EPTI *versus* BI + PBO), month (Month 1: Weeks 1-4), country, and previous treatment failures (≤2; >2) as factors. The interaction terms treatment-by-month and previous treatment failures-by-month as well as number of MMDs at Baseline-by-month were included.

For all key secondary endpoints, the treatment effect favoured eptinezumab 100 mg as add-on to BI *versus* placebo as add-on to BI ($p < 0.0001$).

Participants showed greater reductions in MMDs (Weeks 1-12), MHDs (Weeks 1-4, Weeks 1-12), MAMDs (Weeks 1-4, Weeks 1-12), and average daily pain assessment score (Weeks 1-2) in the eptinezumab group *versus* the placebo group. Larger proportions of participants no longer fulfilling the diagnostic criteria for CM and MOH across Weeks 1-4

(37.8% with eptinezumab *versus* 18.1% with placebo) and Weeks 1-12 (27.2% with eptinezumab *versus* 12.7% with placebo).

Testing Strategy Results – Key Secondary Endpoints (FAS)

Endpoints	Weeks	Placebo-Controlled Period			
		BI + EPTI (N = 302)	BI + PBO (N = 300)		
		LS Mean (SE)[a]/ Proportion		Difference Between BI + EPTI and BI + PBO[b] (95% CI) / OR (95% CI)	p-values
Since p-value was <0.05 for the primary endpoint, the testing continued as follows					
Change from Baseline in MMDs	Weeks 1-12	-7.44 (0.508)	-4.50 (0.508)	-2.94 (-3.86, -2.02)	<0.0001
Since p-value was <0.05, the testing continued as follows					
Change from Baseline in number of MHDs	Weeks 1-4	-6.54 (0.502)	-3.40 (0.502)	-3.15 (-4.07, -2.22)	<0.0001
Since p-value was <0.05, the testing continued as follows					
Change from Baseline in number of MHDs	Weeks 1-12	-7.38 (-3.83, -2.02)	-4.45 (0.497)	-2.93 (-3.83, -2.02)	<0.0001
Since p-value was <0.05, the testing continued as follows					
Proportion of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH	Weeks 1-4	37.8	18.1	3.26 (2.18, 4.94)	<0.0001
Since p-value was <0.05, the testing continued as follows					
Proportion of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH	Weeks 1-12	27.2	12.7	3.05 (1.93, 4.90)	<0.0001

Endpoints	Weeks	Placebo-Controlled Period			
		BI + EPTI (N = 302)	BI + PBO (N = 300)		
		LS Mean (SE)[a]/ Proportion		Difference Between BI + EPTI and BI + PBO[b] (95% CI) / OR (95% CI)	p-values
Since p-value was <0.05, the testing continued as follows					
Change from Baseline in average Daily Pain assessment score	Weeks 1-2	-0.58 (0.048)	-0.27 (0.048)	-0.31 (-0.39, -0.22)	<0.0001
Since p-value was <0.05, the testing continued as follows					
Change from Baseline in MAMDs	Weeks 1-4	-11.32 (0.508)	-7.69 (0.509)	-3.63 (-4.59, -2.67)	<0.0001
Since p-value was <0.05, the testing continued as follows					
Change from Baseline in MAMDs	Weeks 1-12	-11.18 (0.490)	-7.83 (0.490)	-3.35 (-4.23, -2.48)	<0.0001

BI = brief educational intervention; CM = chronic migraine; EPTI = eptinezumab 100 mg; FAS = full-analysis set; MAMD = monthly days with acute headache medication use; MHD = monthly headache day; MOH = medication overuse headache; MMD = monthly migraine day; MMRM = mixed model for repeated measures; OR = odds ratio; PBO = placebo

a Continuous variables are presented using least squares means (SE); response variables are presented using percentages.

b Continuous variables are presented using least squares means and CIs; response variables are presented using ORs and CIs.

The results of the secondary and exploratory endpoints based on continuous and binary eDiary-derived endpoints, were consistent with the results from the analyses of the primary and key secondary endpoints.

The proportion of participants with ≥50% reduction in MMDs from Baseline to Weeks 1-12 was 40.4% in the eptinezumab group and 18.0% in the placebo group. The proportion of participants with ≥75% reduction in MMDs from Baseline to Weeks 1-12 was 12.9% in the eptinezumab group and 5.3% in the placebo group.

On the first day after dosing (Day 1), a smaller proportion of participants reported migraine ($p < 0.0001$) in the eptinezumab group *versus* the placebo group.

Participants in the eptinezumab group had significant reduction in migraine attacks and headache episodes associated with severe pain intensity *versus* participants in the placebo group (Weeks 1-12).

Participants in the eptinezumab group showed greater improvement in Patient Global Impression of Change (PGIC), and MBS scores, HADS sub-scores for depression and anxiety and SDS:H score *versus* participants in the placebo group at Week 12.

The results of the pharmacoeconomic endpoints in the Placebo-controlled Period (Weeks 1-12) showed an efficacy of eptinezumab *versus* placebo with respect to the participant's ability to function normally (based on HIT-6), including daily life activities (based on mMIDAS), quality of life (based on MSQ v2.1), well-being (based on EQ-5D-5L VAS), work productivity and activity impairment (based on WPAI:M) and satisfaction with treatment (based on Treatment Satisfaction Questionnaire for Medicine – 9 items [TSQM-9] scores).

The migraine specific HCRU data showed similar results for eptinezumab *versus* placebo in the Placebo-controlled Period.

Open-label Period

Both treatment sequence groups showed reductions from Baseline in MMDs, MHDs, MAMDs and pain severity Weeks 13-24. A similar proportion of participants in both treatment sequence groups (39% in the PBO-EPTI *versus* 40% in the EPTI-EPTI treatment sequence groups) no longer met the ICHD-3 diagnostic criteria for CM and MOH Weeks 13-24.

Participants in both treatment sequence groups showed similar PGIC and MBS improvement scores at Week 24.

Participants in the EPTI-EPTI treatment sequence group showed numerically greater improvement from Baseline to Week 24 in the HADS sub-scores *versus* the PBO-EPTI treatment sequence group.

Results in both treatment sequence groups were comparable for the pharmacoeconomic endpoints and showed improvement from Baseline to Week 24 in the participant's ability to function normally (based on HIT-6), daily life activities (based on mMIDAS), quality of life (based on MSQ v2.1), well-being (based on EQ-5D-5L VAS), and work productivity (based on WPAI:M).

The TSQM-9 score obtained at Week 24 was similar in both treatment sequence groups.

The migraine specific HCRU showed similar results for both treatment sequence groups at Week 24.

Overall Efficacy and Pharmacoeconomics Summary

The trial met the primary endpoint, with a statistically significant greater mean change from Baseline in MMDs at Weeks 1-4 with eptinezumab 100 mg as add-on to BI *versus* placebo as add-on to BI.

The trial also met all key secondary endpoints, and the vast majority of the secondary efficacy and ePRO endpoints, with eptinezumab demonstrating efficacy in reducing CM and MOH burden *versus* placebo during Weeks 1-4, sustained through Weeks 1-12.

Furthermore, improvements observed during the Placebo-controlled Period were generally sustained during the Open-label Period for participants initially treated with eptinezumab, with similar levels of improvement gained during the Open-label Period for those initially receiving placebo.

Safety Results

Placebo-Controlled Period

During the Placebo-controlled Period, the overall incidence of treatment-emergent adverse event (TEAEs) was 42% in the eptinezumab 100 mg group and 37% in the placebo group.

A total of 15.2% and 12.0% participants in the eptinezumab 100 mg and the placebo groups, respectively reported TEAEs related to IMP.

The overall incidences of serious adverse event (SAEs), TEAEs leading to withdrawal from treatment and TEAEs leading to infusion interruption were low (all ≤1%).

Overall Summary of Treatment-Emergent Adverse Events During Placebo-Controlled Period (APTS)

	BI + EPTI (N = 303) n (%) [E]	BI + PBO (N = 301) n (%) [E]
TEAEs		
Any TEAEs	127 (41.9) [241]	111 (36.9) [229]
Treatment-emergent SAEs	2 (0.7) [3]	1 (0.3) [1]
TEAE intensity		
Mild	70 (23.1) [154]	64 (21.3) [148]
Moderate	50 (16.5) [75]	41 (13.6) [73]
Severe	7 (2.3) [12]	6 (2.0) [8]
TEAEs leading to withdrawal from treatment	1 (0.3) [1]	3 (1.0) [5]
TEAEs leading to infusion interruption	2 (0.7) [2]	1 (0.3) [1]
TEAEs leading to death	0	0
IMP-Related TEAEs		
Any TEAEs	46 (15.2) [64]	36 (12.0) [48]
Treatment-emergent SAEs	0	0
TEAE intensity		
Mild	26 (8.6) [43]	23 (7.6) [31]
Moderate	20 (6.6) [21]	9 (3.0) [13]
Severe	0	4 (1.3) [4]
TEAEs leading to withdrawal from treatment	0	0
TEAEs leading to infusion interruption	2 (0.7) [2]	1 (0.3) [1]
TEAEs leading to death	0	0

APTS = all-patients-treated set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; IMP = investigational medicinal product; PBO = placebo; TEAE = treatment-emergent adverse event

Notes: n represents the number of participants at each level of summarisation. [E] Represents the number of events at each level of summarisation.

An AE was considered causally related to the use of the IMP when the causality assessment by the investigator was probable or possible. If the causality assessment was missing, the AE was considered causally related. If the intensity of an AE was missing, the AE was reported as 'Severe'. At each level of summarisation, a participant was counted once if the participant reported one or more events. For summarisation by Intensity, a participant was counted once under the most severe event.

The system organ class (SOC) with the highest incidence of TEAEs (19.1% in the eptinezumab 100 mg group *versus* 17.6% in the placebo group) was *infections and infestations*. Within all the other SOCs, the incidences of TEAEs did not exceed 7.5% in any group. The incidences of TEAEs within SOCs were generally similar across groups.

TEAEs with incidence ≥2% were (eptinezumab 100 mg *versus* placebo): *nasopharyngitis* (5.0% *versus* 5.6%), *influenza* (3.6% *versus* 3.3%), *dizziness* (2.6% *versus* 3.0%), and *fatigue* (2.0% *versus* 3.7%).

Summary of Treatment-Emergent Adverse Events with Incidence ≥2% in Any Treatment Group by Preferred Term during Placebo-Controlled Period (APTS)

Preferred Term	BI + EPTI (N = 303) n (%)	BI + PBO (N = 301) n (%)
Number of participants with any TEAE with incidence ≥2% in any treatment group	36 (11.9)	40 (13.3)
Nasopharyngitis	15 (5.0)	17 (5.6)
Influenza	11 (3.6)	10 (3.3)
Dizziness	8 (2.6)	9 (3.0)
Fatigue	6 (2.0)	11 (3.7)

APTS = all-patients-treated set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; PBO = Placebo; TEAE = treatment-emergent adverse event

Notes: At each level of participant summarisation, a participant was counted once if the participant reported one or more events.

n represents the number of participants at each level of summarisation.

AEs were coded using MedDRA Version 27.0

The overall incidence of treatment-emergent adverse events of special interest (AESIs) was low (4.3% in the eptinezumab 100 mg group and 3.0% in the placebo group). The most common AESI was *events potentially associated with IMP infusion* and occurred in 2.6% participants in the eptinezumab 100 mg group and 1.0% participants in the placebo group. AESIs of *cardio-/cerebrovascular events* (including hypertension) occurred in 0.3% participants in the eptinezumab 100 mg group and 1.0% participants in the placebo group. All AESIs were non-serious. All the events were *mild* except for 1 event of *severe venous thrombosis limb* in the placebo group.

No participants died during the Placebo-Controlled Period. Two (0.7%) participants in the eptinezumab 100 mg group and 1 (0.3%) participant in the placebo group reported treatment-emergent SAEs, none of which were related to the IMP. One (0.3%) participant in the eptinezumab 100 mg group and 3 (1.0%) participants in the placebo group reported TEAEs leading to withdrawal from treatment, none of which were related to IMP.

Events that led to withdrawal of treatment were non-serious and *mild* to *moderate* in intensity, with one exception in the eptinezumab 100 mg group: 1 participant reported *breast cancer recurrent* which was serious and *severe*.

Open-label Period

During the Open-label Period, the overall incidence of TEAEs was 30% in the EPTI-EPTI and 34% in the PBO-EPTI treatment sequence groups.

A total of 6.3% and 14.7% participants in the EPTI-EPTI and PBO-EPTI treatment sequence groups, respectively, reported TEAEs related to IMP.

The overall incidences of SAEs, TEAEs leading to withdrawal from treatment, and the TEAEs leading to infusion interruption were low (all <2%).

Overall Summary of Treatment-Emergent Adverse Events per Treatment Sequence Group During the Open-Label Period (APTS-OL)

	BI + EPTI-EPTI (N = 300) n (%) [E]	**BI + PBO-EPTI (N = 293) n (%) [E]**
Treatment-Emergent Adverse Event		
Any TEAEs	91 (30.3) [162]	101 (34.5) [199]
Treatment-Emergent SAEs	2 (0.7) [4]	5 (1.7) [7]
TEAE Intensity		
Mild	47 (15.7) [93]	56 (19.1) [123]
Moderate	40 (13.3) [62]	41 (14.0) [69]
Severe	4 (1.3) [7]	4 (1.4) [7]
TEAEs Leading to Withdrawal from Treatment	0	5 (1.7) [5]
TEAEs Leading to Infusion Interruption	1 (0.3) [1]	1 (0.3) [1]
TEAEs Leading to Death	0	0
IMP-Related TEAEs		
Any TEAEs	19 (6.3) [24]	43 (14.7) [66]
Treatment-Emergent SAEs	0	0
TEAE Intensity		
Mild	8 (2.7) [10]	30 (10.2) [49]
Moderate	11 (3.7) [14]	13 (4.4) [17]
Severe	0	0
TEAEs Leading to Withdrawal from Treatment	0	4 (1.4) [4]
TEAEs Leading to Infusion Interruption	1 (0.3) [1]	1 (0.3) [1]
TEAEs Leading to Death	0	0

	BI + EPTI-EPTI (N = 300) n (%) [E]	BI + PBO-EPTI (N = 293) n (%) [E]

APTS-OL = all-patients-treated-open-label set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; IMP = investigational medicinal product; PBO = placebo

Notes: n represents the number of participants at each level of summarisation. [E] Represents the number of events at each level of summarisation.

An AE was considered causally related to the use of the IMP when the causality assessment by the investigator was probable or possible. If the causality assessment was missing, the AE was considered causally related. If the intensity of an AE was missing, the AE was reported as 'Severe'. At each level of summarisation, a participant was counted once if the participant reported one or more events. For summarisation by Intensity, a participant was counted once under the most severe event.

AEs were coded using MedDRA Version 27.0.

The SOC with the highest incidence of TEAEs (11.0% in EPTI-EPTI *versus* 11.3% in PBO-EPTI treatment sequence group) was *infections and infestations*. Within all the other SOCs, the incidences of TEAEs did not exceed 7.5% in any treatment sequence group. The incidences of TEAEs within SOCs were generally similar across treatment sequence groups.

The TEAEs with incidence ≥2% was also similar between both treatment sequence groups (EPTI-EPTI *versus* PBO-EPTI): *influenza* (2.3% *versus* 2.0%) and *nasopharyngitis* (2.3% *versus* 3.4%).

Summary of Treatment-Emergent Adverse Events with Incidence ≥2% in Any Treatment Sequence Group by Preferred Term during the Open-Label Period (APTS-OL)

Preferred Term	BI + EPTI-EPTI (N = 300) n (%)	BI + PBO-EPTI (N = 293) n (%)
Influenza	7 (2.3)	6 (2.0)
Nasopharyngitis	7 (2.3)	10 (3.4)

APTS-OL = all-patients-treated-open-label set; BI = brief educational intervention; EPTI = eptinezumab 100 mg; IMP = investigational medicinal product; PBO = placebo

Notes: At each level of participant summarisation, a participant was counted once if the participant reported one or more events.

n represents the number of participants at each level of summarisation.

AEs were coded using MedDRA, Version 27.0

The overall incidence of treatment-emergent AESIs was low (2.3% in the EPTI-EPTI and 7.2% in the PBO-EPTI treatment sequence groups). The most common AESI was *hypersensitivity and anaphylactic reactions* and occurred in 1.3% participants in the EPTI-EPTI treatment sequence group and in 3.4% participants in the PBO-EPTI treatment sequence group. All AESIs of *hypersensitivity and anaphylactic reactions* were non-serious

and *mild or moderate* in intensity. Two AESIs of *transient ischaemic attack* and *suicide attempt* were serious. Both were considered not related to IMP.

No participants died during the Open-label Period. Two (0.7%) participants in the EPTI-EPTI and 5 (1.7%) participants in the PBO-EPTI treatment sequence groups reported treatment-emergent SAEs. All treatment-emergent SAEs were considered not related to the IMP. Five (1.7%) participants in the PBO-EPTI treatment sequence group reported TEAEs leading to withdrawal from treatment. None of the participants reported TEAEs leading to withdrawal from treatment in the EPTI-EPTI treatment sequence group.

Events that led to withdrawal of treatment were non-serious and *mild* to *moderate* in intensity.

Overall Safety Summary

Eptinezumab 100 mg was generally well-tolerated, with no new safety signals identified. The incidences of SAEs, TEAEs leading to withdrawal from treatment, and AESIs were low. No participants died during the trial.

Immunogenicity Results

The development of anti-drug antibodies/neutralizing antibodies was not evaluated in this trial. The immunogenicity of eptinezumab has previously been established in the clinical development programme with eptinezumab for preventive treatment of migraine.

Conclusions

The results show that treatment with eptinezumab 100 mg as add-on to BI compared to placebo as add-on to BI is effective in preventing migraine, reducing the use of acute headache medication, reducing migraine-related burden and impact, and improving work productivity and health related quality of life in people with a dual diagnosis of CM and MOH.

Statistically significant treatment effects ($p < 0.0001$) favouring eptinezumab 100 mg as add-on to BI *versus* placebo as add-on to BI were seen for the primary and all key secondary efficacy endpoints.

In the primary analysis of the primary endpoint (the mean change from Baseline in MMDs [Weeks 1-4]), eptinezumab 100 mg as add on to BI demonstrated a clinically meaningful difference *versus* placebo as add on to BI (-6.85 days and -3.66 days, respectively; $p < 0.0001$). The results of the sensitivity analyses of the primary endpoint were consistent with the results of the primary analysis.

For all key secondary endpoints, eptinezumab was statistically significantly favoured *versus* placebo ($p < 0.0001$): participants treated with eptinezumab reported a reduction in pain severity Weeks 1-2, alongside reductions in MMDs, MHDs, and MAMDs, and larger

proportions of participants no longer fulfilling the diagnostic criteria for CM and MOH across Weeks 1-4 and Weeks 1-12.

For the vast majority of the eDiary-derived secondary efficacy endpoints, improvements with eptinezumab were observed as early as Weeks 1-4 (for endpoints with 4-week assessment timepoints) and sustained through Weeks 1-12 *versus* placebo.

Greater improvements were observed with eptinezumab *versus* placebo across multiple ePROs measuring the ability to function normally (HIT-6), pursue daily life activities (mMIDAS), quality of life (MSQ v2.1), well-being (EQ-5D-5L VAS), work productivity and activity impairment (WPAI:M), and satisfaction with treatment (TSQM-9).

Furthermore, improvements observed during the Placebo-controlled Period were generally sustained during the Open-label Period for participants initially treated with eptinezumab, with similar levels of improvement gained during the Open-label Period for those initially receiving placebo.

Eptinezumab 100 mg was generally well-tolerated. The safety and tolerability profiles were comparable to those observed previously with eptinezumab in participants with migraine, and no new safety signals were identified.