Synopsis – Trial 19140A

Trial Title Interventional, randomized, double-blind, parallel-group, placebo-controlled trial to evaluate efficacy and safety of eptinezumab for the preventive treatment of migraine
Investigators 87 principal investigators at 84 sites in Asia and Europe *Signatory Investigator* – [redacted]
Trial Sites 84 sites – 18 in Greater China (15 in mainland and 3 in Taiwan), 7 in Georgia, 27 in Japan, 9 in Poland, 9 in Republic of Korea, 4 in Slovakia, 10 in Spain
Publications Yu S, Matsumori Y, Kim BK, Gryglas-Dworak A, Giorgadze G, Pozo-Rosich P, et al. Efficacy and safety of eptinezumab in a predominantly Asian population with chronic migraine: Results of the randomized, double-blind, placebo-controlled SUNRISE trial. Cephalalgia. 2025;45(10):1–13.
Trial Period *First participant first visit* – 29 May 2021 (the date when the first *Informed Consent Form* was signed) *Last participant last visit* – 17 February 2025 (the date of the last protocol-specified contact with any participant)
Report Dates 4 December 2025 (Addendum 1) 28 March 2025 (Integrated Clinical Trial Report)
This trial was conducted in compliance with *Good Clinical Practice*.

Objectives, Endpoints, and Estimands

Primary Objective	Endpoints
• To evaluate the efficacy of eptinezumab for the prevention of CM	• Primary endpoint: – change from Baseline in the number of MMDs (Weeks 1-12) • Key secondary endpoints: – response: ≥50% reduction from Baseline in MMDs (Weeks 1-12) – response: ≥75% reduction from Baseline in MMDs (Weeks 1-4) – response: ≥75% reduction from Baseline in MMDs (Weeks 1-12) – migraine rate on the day after dosing (Day 1) • Secondary endpoints: – response: ≥50% reduction from Baseline in MHDs (Weeks 1-12) – change from Baseline in the number of MHDs (Weeks 1-12) – response: ≥75% reduction from Baseline in MHDs (Weeks 1-4) – change from Baseline in rate of migraines with severe pain intensity (Weeks 1-12) – change from Baseline in rate of headaches with severe pain intensity (Weeks 1-12) – change from Baseline in the number of MMDs with use of acute medication (Weeks 1-12) – PGIC score at Week 12 – MBS score at Week 12, as measured relative to Screening • Exploratory endpoints: – change from Baseline in monthly number of migraine attacks (Weeks 1-12) – change from Baseline in monthly number of headache episodes (Weeks 1-12) – response: 100% reduction from Baseline in MHDs (average of 4-weekly results over Weeks 1-12) – response: 100% reduction from Baseline in MMDs (average of 4-weekly results over Weeks 1-12)

Primary Objective	Endpoints
Primary Estimand: • The primary estimand was the mean difference in change from Baseline in number of MMDs across Weeks 1-12 in patients with CM treated with eptinezumab and placebo with or without the use of preventive migraine treatment in the hypothetical scenario where no other long-acting anti-CGRPs were available and regardless of infusion interruption or termination before full dose was received. • The estimand for the primary endpoint was described by the following attributes: – The population of interest was patients with CM. – The endpoint to be considered was the change from Baseline in MMDs across Weeks 1-12. – The treatment condition of interest was the comparison of eptinezumab 100 mg and 300 mg to placebo with or without the use of other preventive migraine medication except other anti-CGRPs, and without the use of other anti-CGRPs. – The intercurrent event use of other long-acting anti-CGRPs to treat a migraine was addressed using a hypothetical strategy. – The intercurrent event infusion interruption or termination before full dose was received was addressed using a treatment policy strategy. – The population level summary was the mean difference in the primary endpoint across Weeks 1-12. **Estimands for the Key Secondary Endpoints**: • ≥50% response: The odds ratio for the proportion of patients with ≥50% reduction in MMDs (Weeks 1-12) in patients with CM, treated with eptinezumab and placebo, with or without use of other preventive migraine treatment, and regardless of infusion interruption or termination before full dose was received. • Response: Estimands for the other key secondary endpoints based on response variables were defined similarly to the estimand for ≥50% response. • Migraine rate Day 1: The difference in proportion of patients with a migraine reported on the day after dosing (Day 1) in patients with CM, treated with eptinezumab and placebo, with or without use of other preventive migraine treatment, and regardless of infusion interruption or termination before full dose was received.	

CGRP = calcitonin gene-related peptide; CM = chronic migraine; MBS = most bothersome symptom; MHD = monthly headache day; MMD = monthly migraine day; PGIC = Patient Global Impression of Change

Secondary Objective	Endpoints
• To evaluate the efficacy of eptinezumab on health-related quality of life, Health Care Resource Utilization, and work productivity	• Secondary endpoints: – change from Baseline to Week 12 in the HIT-6 score – change 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 12 in the EQ-5D-5L VAS score – HCRU at Baseline and Week 12 – change from Baseline to Week 12 in the WPAI:M Questionnaire sub-scores (*Absenteeism*, *Presenteeism*, *Work productivity loss*, *Activity impairment*)

EQ-5D-5L = Health-related Quality of Life; HCRU = Health Care Resources Utilization; HIT-6 = Headache Impact Test-6; MSQ v2.1 = Migraine-Specific Quality of Life; VAS = Visual Analogue Scale; WPAI:M = Work Productivity and Activity Impairment: Migraine

Exploratory Objective	Endpoints
• To evaluate the exposure of eptinezumab	• Eptinezumab plasma concentrations after infusion and at Week 12

Safety Objective	Endpoints
• To evaluate the safety and tolerability of eptinezumab	• Adverse events • Absolute values and changes from Baseline in clinical safety laboratory test values, vital signs, weight, and ECG parameter values • Potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Development of specific ADAs including NAbs • C-SSRS score

ADA = anti-drug (eptinezumab) antibody; C-SSRS = Columbia-Suicide Severity Rating Scale; NAb = neutralizing anti-drug antibody

Trial Methodology

This was an interventional, prospective, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled, phase III trial.

The total trial duration from the Screening Visit to the Safety Follow-up Visit was approximately 36 weeks. The trial consisted of:

- Screening Period – 28 to 30 days
- Placebo-controlled Period (double-blind) – 12 weeks
- Extension Period (dose-blind) – 12 weeks
- Safety Follow-up Period – 8 weeks

In Japan, participants recruited under the Japanese edition of the *Clinical Trial Protocol*, Edition 2.0, who completed the Placebo-controlled Period of the Lead-in Trial 19140A had the option to continue in a 68-week Open-label Extension Trial (Trial 19140B) in which all participants received eptinezumab. These participants entered directly into the Open-label Extension Trial 19140B without participation in the Extension Period of Trial 19140A. As the targeted number of participants necessary for evaluating 12 months of safety data (Trial 19140B) in Japan had been achieved, the Japanese participants recruited under the *Clinical Trial Protocol* of Trial 19140A (Edition 3.0, dated 19 October 2022) did not enter the Open-label Extension Trial 19140B but instead continued in the Extension Period of Trial 19140A.

At Baseline, the participants were randomly allocated to one of the three treatment groups for the Placebo-controlled Period in a ratio of 1:1:1: placebo, eptinezumab 100 mg, or eptinezumab 300 mg. In addition, at Baseline, participants who were assigned to placebo in the

Placebo-controlled Period were randomly allocated to one of the two dose-blinded treatment groups for the Extension Period in a ratio of 1:1: eptinezumab 100 or 300 mg. Participants who were assigned to eptinezumab in the Placebo-controlled Period received the same treatment in the Extension Period. Randomization was stratified by location and by monthly migraine days (MMDs) at Baseline (MMDs<17 *versus* MMDs≥17).

At the Baseline Visit, participants received investigational medicinal product (IMP) by intravenous (IV) infusion over a period of 30(+15) minutes.

At the Primary Outcome Visit (Week 12), participants could enter the Extension Period and received a second dose-blinded IMP IV infusion according to the treatment assignment at Baseline.

The participants attended a Safety Follow-up Visit (Week 32), 8 weeks after the End-of-Treatment Visit. The participants who withdrew, except for those who withdrew their consent, were asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-up Visit at 20 weeks after the last administration of IMP.

An independent safety Data Monitoring Committee (DMC) regularly monitored the participants' safety data according to the DMC Charter.

In the Placebo-controlled Period, the treatment groups are named as follows:
- Placebo (PBO) – participants who received placebo in the Placebo-controlled Period
- eptinezumab 100 mg (EPTI100) – participants who received eptinezumab 100 mg in the Placebo-controlled Period
- eptinezumab 300 mg (EPTI300) – participants who received eptinezumab 300 mg in the Placebo-controlled Period

In the Extension Period, the treatment groups are named as follows:
- PBO-EPTI100 – participants who received placebo in the Placebo-controlled Period and eptinezumab 100 mg in the Extension Period
- PBO-EPTI300 – participants who received placebo in the Placebo-controlled Period and eptinezumab 300 mg in the Extension Period
- EPTI100-EPTI100 – participants who received eptinezumab 100 mg in both the Placebo-controlled Period and the Extension Period
- EPTI300-EPTI300 – participants who received eptinezumab 300 mg in both the Placebo-controlled Period and the Extension Period
- Total – participants who received placebo or eptinezumab 100 or 300 mg in the Placebo-controlled Period and eptinezumab 100 or 300 mg in the Extension Period

Number of Participants Planned

A total of 945 participants were planned for randomization: 315 in the PBO group, 315 in the EPTI100 group, and 315 in the EPTI300 group.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of chronic migraine defined by International Headache Society International Classification of Headache Disorders guidelines and a history of migraine onset at least 12 months prior to the Screening Visit, who:

- had a migraine onset at ≤50 years of age
- had ≥8 migraine days per month for each month within the past 3 months prior to the Screening Visit
- fulfilled the following criteria for migraine in prospectively collected information in the electronic diary (eDiary) during the Screening Period
  - migraine occurring on ≥8 days and headache occurring on ≥15 to ≤26 days
- had demonstrated compliance with the eDiary by entry of data for at least 24 of the 28 days following the Screening Visit
- were aged ≥18 (≥20 for Taiwan) and ≤75 years at the Screening Visit

The individuals with confounding and clinically significant pain syndromes or a history or diagnosis of other primary headache disorders and individuals who received any medication targeting the calcitonin gene-related peptide pathway for preventive treatment of migraine were excluded.

Individuals with concurrent medication overuse headache (MOH) diagnosis were allowed to enrol.

Investigational Medicinal Products (IMPs), Doses, and Modes of Administration

Eptinezumab – 100 mg/mL; concentrate for solution for infusion, IV

Participants allocated to the EPTI100 group received 1x 100 mg concentrate for solution for infusion 100 mg/mL added to 100 ml of 0.9% normal saline, IV.

Participants allocated to the EPTI300 group received 3x 100 mg concentrate for solution for infusion 100 mg/mL added to 100 ml of 0.9% normal saline, IV.

Control Product, Dose, and Mode of Administration

Placebo – 0.9% normal saline (prepared on site), IV

Participants allocated to the PBO group received 100 mL of 0.9% saline solution, IV.

Duration of Treatment

Placebo-controlled Period – 12 weeks; Extension Period – 12 weeks

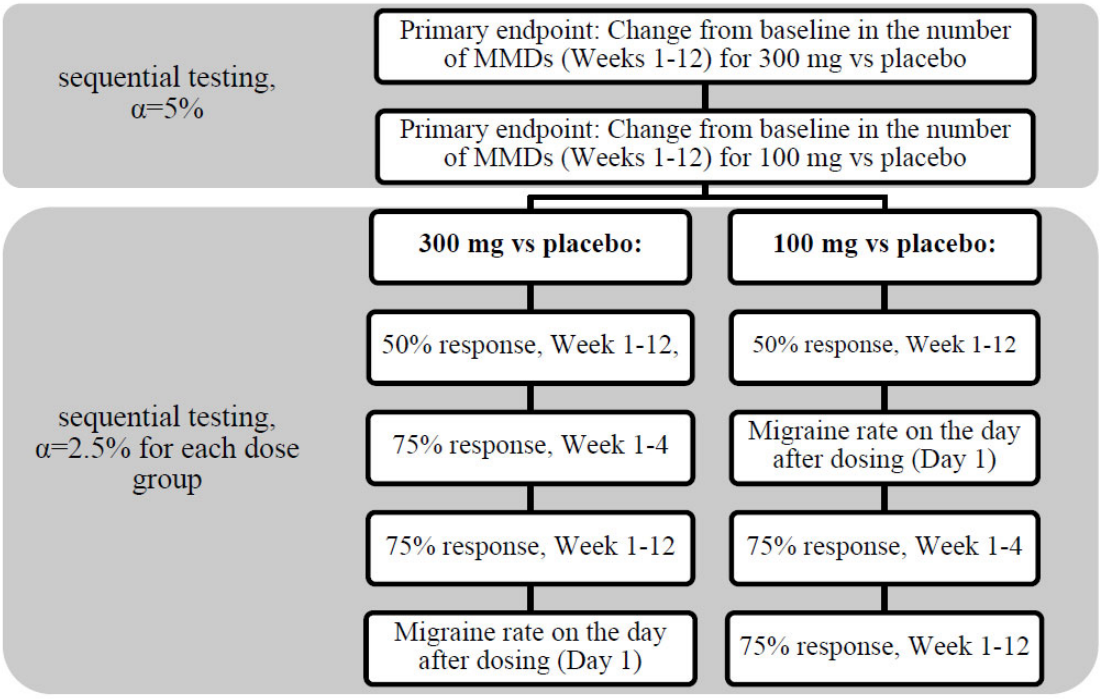
Statistical Methodology

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

- *all-participants-randomized set* (APRS) – all randomized participants
- *all-participants-treated set* (APTS) – all participants in the APRS who received an infusion of the double-blind IMP
- *full-analysis set* (FAS) – all participants in the APTS who had a valid assessment of Baseline MMDs and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12
- *all-participants-treated set – Extension Period* (APTS-EX) – all participants in the APRS who received an infusion of the IMP in the Extension Period
- *all-participants-treated set – Follow Up* (APTS-FU) – all participants in the APTS who were not in the APTS-EX, and who had data collected from the Safety Follow-up Visit

Unless otherwise specified, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS. All the p-values were based on two-sided tests; the confidence intervals (CIs) are two-sided; and the endpoints not included in the testing strategy are presented with descriptive p-values and 95% CIs.

A combination of sequential testing and splitting of the significance level by dose was applied. For each step, the treatment effect was tested on the specified significance level and testing was only continued if all prior effects in the hierarchy had p-values below the specified significance levels:



MMD = monthly migraine day

The main estimator for the primary endpoint, change from Baseline in MMDs (Weeks 1-12), was estimated using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) approach. The analyses were performed on MMDs by month using an MMRM, with month defined as 4-week intervals (Weeks 1-4, Weeks 5-8, Weeks 9-12), with Baseline MMDs as a continuous covariate, and treatment, month, and location as fixed factors. In addition, the model included treatment-by-month interaction, and Baseline MMDs-by-month interaction. An unstructured variance structure was used to model the within-participant errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

The change from Baseline in MMDs (Weeks 1-12) was estimated as the average across the three 4-week intervals, and the treatment effect of eptinezumab was calculated from the least squares estimates from the MMRM model for the treatment-by-month interaction *via* a contrast for each of 2 doses of eptinezumab compared to placebo.

The 3 key secondary endpoints, response defined as ≥50% reduction from Baseline in MMDs (Weeks 1-12), response defined as ≥75% reduction from Baseline in MMDs (Weeks 1-4), and response defined as ≥75% reduction from Baseline in MMDs (Weeks 1-12) were analysed using logistic regression. The model included Baseline MMDs as a continuous covariate, and treatment as a factor.

Migraine on the day after dosing (Day 1) was analyzed using an extended Cochran-Mantel-Haenszel test, adjusting for the stratification factor (MMDs <17, MMDs ≥17 at Baseline).

Participant Disposition and Analysis Sets

Placebo-controlled Period

Participant disposition for the Placebo-controlled Period is summarized below:

	PBO		EPTI100		EPTI300		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants randomized	328		328		327		983	
Participants treated (APTS)	325		327		326		978	
Participants completed	314	96.6%	316	96.6%	309	94.8%	939	96.0%
Participants withdrawn	11	3.4%	11	3.4%	17	5.2%	39	4.0%
Primary reason for withdrawal								
Adverse events	1	0.3%	4	1.2%	4	1.2%	9	0.9%
Lack of efficacy	1	0.3%	0	0	0	0	1	0.1%
Protocol violation	0	0	0	0	2	0.6%	2	0.2%
Withdrawal of consent	4	1.2%	3	0.9%	5	1.5%	12	1.2%
Other	5	1.5%	4	1.2%	6	1.8%	15	1.5%
Analysis sets								
APTS	325		327		326		978	
FAS	325		323		324		972	

APTS = all-participants-treated set; EPTI = eptinezumab; FAS = full-analysis set; PBO = placebo

Extension Period

Participant disposition for the Extension Period is summarized below:

	PBO-EPTI100		PBO-EPTI300		EPTI100-EPTI100		EPTI300-EPTI300		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants treated (APTS-EX)	128		131		262		256		777	
Participants completed Extension Period	122	95.3%	130	99.2%	250	95.4%	245	95.7%	747	96.1%
Participants withdrawn	6	4.7%	1	0.8%	12	4.6%	11	4.3%	30	3.9%
Primary reason for withdrawal										
Adverse events	2	1.6%	0	0	0	0	0	0	2	0.3%
Lack of efficacy	0	0	0	0	0	0	1	0.4%	1	0.1%
Withdrawal of consent	3	2.3%	1	0.8%	7	2.7%	2	0.8%	13	1.7%
Lost to follow-up	1	0.8%	0	0	0	0	2	0.8%	3	0.4%
Other	0	0	0	0	5	1.9%	6	2.3%	11	1.4%

APTS-EX = all-participants-treated set — Extension Period; EPTI = eptinezumab; PBO = placebo

Demographics and Baseline Characteristics of the Trial Population

Overall, the treatment groups were comparable with respect to demographics. The mean age of the participants was 42 years, and the majority of the participants were women (86%) and enrolled in sites in Asia (64%), primarily in Japan (31%) and Greater China (23%). Most participants were in the age subgroup >35 years old (72%). The mean height, weight, and body mass index (BMI) were 163 cm (ranging from 139 to 192 cm), 63 kg (ranging from 35 to 110 kg), and 24 kg/m^2 (ranging from 15 to 39 kg/m^2), respectively.

The treatment groups were comparable with respect to migraine history and Baseline disease characteristics.

Based on the eDiary data collected during the Screening Period, the mean number of MMDs was 17 for the PBO group, 18 for the EPTI100 group, and 17 for the EPTI300 group. The mean number of monthly headache days (MHDs) was 20 in each treatment group.

At Baseline, the most common most bothersome symptoms (MBS) were *pain with activity* (24%), *nausea* (19%), and *sensitivity to light* (14%).

The mean Baseline Headache Impact Test-6 (HIT-6) score was 65 points (a score ≥60 points indicates severe impact of headache on the participants' ability to function normally in daily life) in each treatment group. The 3 mean Baseline for Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1) sub-scores ranged from 43 to 44 points for *MSQ Role Function-Restrictive*; 58 to 59 points for *MSQ Role Function-Preventative*; and 55 to 57 points for *MSQ Emotional Function* (each MSQ v2.1 sub-score was out of 100 points). The mean Baseline Health-related Quality of Life (EQ-5D-5L) Visual Analogue Scale (VAS) score

ranged from 70 to 72 points and reflects the impact of migraine on overall quality of life. The majority of participants did not visit a doctor or general practitioner (73%) within 4 weeks prior to the Baseline Visit. The Baseline work productivity loss and activity impairment was substantial (ranged from 55 to 60 out of 100 points).

Exposure

Placebo-controlled Period

In the Placebo-controlled Period, ≥98% of participants completed their infusion as planned. A total of 7 participants (5 in the EPTI100 group and 2 in the EPTI300 group) did not complete their infusion as planned, that is, the infusion was terminated prematurely and the participants did not receive the full dosage.

Extension Period

In the Extension Period, ≥99% of participants completed their infusion as planned. A total of 2 participants (1 in the PBO-EPTI300 group and 1 in the EPTI300-EPTI300 group) did not complete their infusion as planned, that is, these participants did not receive the full dosage at Visit 5. Two participants received a different dose than planned, that is, 100 mg instead of 300 mg eptinezumab

Efficacy/Pharmacoeconomic Results

In the Placebo-controlled Period, in the primary analysis of the primary endpoint, both doses of eptinezumab demonstrated statistically significant effects relative to placebo ($p<0.0001$). The mean change from Baseline in the number of MMDs (Weeks 1-12) was -4.8 for the PBO group, -7.2 for the EPTI100 group, and -7.5 for the EPTI300 group, and the mean difference *versus* placebo was -2.4 and -2.7 days in the EPTI100 and EPTI300 groups, respectively.

Regarding the key secondary endpoints, both doses of eptinezumab demonstrated a ≥2-fold higher odds ratio (OR) *versus* placebo for ≥50% reduction from Baseline in MMDs (Weeks 1-12, EPTI100: OR = 2.2; EPTI300: OR = 2.7; $p<0.0001$ for both) and ≥75% reduction from Baseline in MMDs (Weeks 1-4, EPTI100: OR = 3.9, EPTI300: OR = 4.4, $p<0.0001$ for both; Weeks 1-12, EPTI100: OR = 2.9, EPTI300: OR = 3.0, $p<0.0001$ for both). Both doses of eptinezumab also demonstrated a lower Day 1 migraine rate compared with placebo ($p<0.01$ for both).

The sequential hierarchy testing by dose that was applied to the efficacy results confirmed the efficacy of eptinezumab, with both doses showing statistically significant advantages over placebo for all key secondary endpoints.

The other secondary endpoints also showed better outcomes for both doses of eptinezumab *versus* placebo for the rate of migraines with severe pain intensity and the number of MMDs with use of acute medication. Additionally, the data for MHDs, headache responder rates, and the rate of headache with severe pain intensity showed better outcomes for both doses of

eptinezumab *versus* placebo. Furthermore, improvements across patient-reported outcomes (PROs; Patient Global Impression of Change [PGIC] and MBS) were greater for both doses of eptinezumab compared to placebo at each timepoint ($p<0.0001$).

The results for the pharmacoeconomic endpoints (HIT-6 score, MSQ v2.1 sub-scores, EQ-5D-5L VAS score, Health Care Resource Utilization [HCRU], and Work Productivity and Activity Impairment: Migraine [WPAI:M] score) consistently showed greater improvements in the EPTI100 and EPTI300 groups than in the PBO group in the Placebo-controlled Period.

Safety Results

Placebo-controlled Period

The overall incidence of treatment-emergent adverse events (TEAEs) was similar between the treatment groups (34% in the PBO group, 38% in the EPTI100 group, and 32% in the EPTI300 group). In all treatment groups, the incidences of serious adverse events (SAEs), TEAEs leading to withdrawal, and TEAEs leading to IMP interruption or termination were low (<2.0% in any treatment group).

The adverse event incidence presented in the 19140A *Clinical Trial Report* is summarized below. However, during the preparation of this *Addendum*, it was discovered that due to a data coding error of adverse events leading to IMP interruption or termination, 4 TEAEs (2 *anaphylactic reactions*, 1 *hypersensitivity*, and 1 *infusion related hypersensitivity reaction*) had, by mistake, not been categorized as TEAEs leading to IMP infusion interruption or termination. Nonetheless, these 4 TEAEs were already reported as TEAEs leading to withdrawal.

	PBO		EPTI100		EPTI300	
	n	(%)	n	(%)	n	(%)
Number of participants	325		327		326	
Participants with TEAEs	109	(33.5)	123	(37.6)	105	(32.2)
Participants with SAEs	4	(1.2)	5	(1.5)	3	(0.9)
Participants with TEAEs leading to withdrawal	2	(0.6)	4	(1.2)	4	(1.2)
Participants with TEAEs leading to infusion interruption or termination	0	0	3	(0.9)	1	(0.3)
Deaths	0		0		0	
Total number of TEAEs	186		185		174	
Total number of SAEs	9		5		4	

EPTI = eptinezumab; PBO = placebo

The only system organ class (SOC) with an incidence of TEAEs ≥5% in any treatment group was *infections and infestations* (18% in the PBO group, 18% in the EPTI100 group, and 15% in the EPTI300 group). The distribution of the TEAEs across the different SOCs was generally similar for all treatment groups.

The most common TEAE was coronavirus disease 2019 (*COVID-19)*, with an incidence of 4.3% in the PBO group, 5.5% in the EPTI100 group, and 4.6% in the EPTI300 group. The

other TEAEs with an incidence ≥2% in any treatment group were *nasopharyngitis*, *upper respiratory tract infection*, and *urinary tract infection*.

TEAEs with an incidence ≥2% in any treatment group are summarized below:

Preferred Term	PBO		EPTI100		EPTI300	
(MedDRA Version 27.0)	n	(%)	n	(%)	n	(%)
Number of participants	325		327		326	
COVID-19	14	(4.3)	18	(5.5)	15	(4.6)
Nasopharyngitis	16	(4.9)	11	(3.4)	11	(3.4)
Upper respiratory tract infection	9	(2.8)	6	(1.8)	6	(1.8)
Urinary tract infection	3	(0.9)	7	(2.1)	5	(1.5)

COVID-19 = coronavirus disease 2019; EPTI = eptinezumab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo

For the majority of participants with TEAEs, the TEAEs were *mild* or *moderate*. The incidence of *severe* TEAEs was 0.9% in all treatment groups. No *severe* TEAE occurred in >1 participant per preferred term in any treatment group.

The overall incidence of treatment-emergent adverse events of special interest (AESIs) was low. Three AESIs of *anaphylactic reaction* (2 in the EPTI100 group and 1 in the EPTI300 group) and 1 AESI of *hypersensitivity* (EPTI100 group) were serious, considered *related* to IMP, and led to participant withdrawal. In addition, 1 non-serious AESI of *infusion related hypersensitivity reaction* (EPTI300 group) led to withdrawal. Furthermore, there were 2 AESIs, 1 of *hepatic function abnormal* (PBO group; considered *related*) and 1 of *suicidal attempt* (EPTI300 group; considered *not related*), that were serious and led to participant withdrawal. All other AESIs were non-serious and did not lead to participant withdrawal.

None of the participants died. A total of 12 participants had treatment-emergent SAEs: 4 in the PBO group, 5 in the EPTI100 group, and 3 in the EPTI300 group. SAEs of *anaphylactic reaction* and *hypersensitivity* occurred in 3 participants in the EPTI100 group and 1 participant in the EPTI300 group. Other SAEs occurred in single participants.

A total of 10 participants, 2 in the PBO group, 4 in the EPTI100 group, and 4 in the EPTI300 group, had TEAEs that led to withdrawal from the trial. *Immune system disorders* including *anaphylactic reactions*, *hypersensitivity*, and *infusion related hypersensitivity reactions* led to withdrawal in 3 participants in the EPTI100 group and 2 participants in the EPTI300 group. Other TEAEs leading to withdrawal occurred in single participants.

A total of 8 participants had TEAEs that led to interruption or termination of the IMP infusion: 5 in the EPTI100 group and 3 in the EPTI300 group. The TEAEs leading to IMP infusion interruption or termination that occurred in >1 participant in any treatment group were *anaphylactic reaction* (2 in the EPTI100 group) and *infusion related hypersensitivity reaction* (2 in the EPTI300 group). Among the TEAEs that led to interruption or termination of the IMP infusion, the events of *anaphylactic reaction* (2 in the EPTI100 group and 1 in the EPTI300 group) and *hypersensitivity* (1 in the EPTI100 group) were SAEs and considered *related* to IMP.

The mean changes from Baseline in the laboratory test values, vital signs, electrocardiogram (ECG) parameters (including shifts in heart-rate corrected QT intervals using Fridericia's correction formula [QTcF]), and body measurement values were generally small and comparable across treatment groups, with no clinically relevant findings. The proportions of participants with post-Baseline potentially clinically significant (PCS) values across the variables were generally low and with no clinically relevant differences between treatment groups.

One participant in the EPTI300 group had a non-fatal *suicide attempt*; this event was an SAE and considered *not related* to IMP. Otherwise, no suicidal ideation or behaviour, as assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS), occurred during the Placebo-controlled Period.

Extension Period

The overall incidence of TEAEs ranged from 36% to 43% across treatment groups and was similar between the treatment groups. In all treatment groups, the incidences of SAEs, TEAEs leading to withdrawal from the trial, and TEAEs leading to IMP interruption or termination were low (<4.0% in any treatment group).

The adverse event incidence is summarized below:

	PBO-EPTI100		PBO-EPTI300		EPTI100-EPTI100		EPTI300-EPTI300	
	n	(%)	n	(%)	n	(%)		
Number of participants	128		131		262		256	
Participants with TEAEs	46	(35.9)	56	(42.7)	111	(42.4)	100	(39.1)
Participants with SAEs	5	(3.9)	3	(2.3)	8	(3.1)	3	(1.2)
Participants with TEAEs leading to withdrawal	2	(1.6)	0		0		0	
Participants with TEAEs leading to infusion interruption or termination	0		2	(1.5)	1	(0.4)	0	
Deaths	0		0		0		0	
Total number of TEAEs	92		94		184		182	
Total number of SAEs	7		3		9		3	

EPTI = eptinezumab; n = number of participants; PBO = placebo

The most common TEAE was *COVID-19*, with an incidence ranging from 6.3% to 9.9% across treatment groups. Other TEAEs with an incidence of ≥2% in any treatment group included *nasopharyngitis*, *upper respiratory tract infection*, *urinary tract infection*, *migraine*, *weight increased*, and *oropharyngeal pain*.

TEAEs with an incidence ≥2% in any treatment group during the Extension Period are summarized below:

Preferred Term	PBO-EPTI100		PBO-EPTI300		EPTI100-EPTI100		EPTI300-EPTI300	
(MedDRA Version 27.0)	n	(%)	n	(%)	n	(%)		
Number of participants	128		131		262		256	
COVID-19	8	(6.3)	13	(9.9)	17	(6.5)	20	(7.8)
Nasopharyngitis	5	(3.9)	4	(3.1)	11	(4.2)	9	(3.5)
Upper respiratory tract infection	3	(2.3)	4	(3.1)	9	(3.4)	6	(2.3)
Urinary tract infection	1	(0.8)	5	(3.8)	6	(2.3)	4	(1.6)
Migraine	2	(1.6)	0		9	(3.4)	2	(0.8)
Weight increased	3	(2.3)	0		3	(1.1)	2	(0.8)
Oropharyngeal pain	0		3	(2.3)	1	(0.4)	1	(0.4)

COVID-19 = coronavirus disease 2019; EPTI = eptinezumab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo

For the majority of participants with TEAEs, the TEAEs were *mild* or *moderate*. The incidence of *severe* TEAEs ranged from 0.8% to 2.7% across treatment groups. The only *severe* TEAE that occurred in >1 participant per preferred term in any treatment group was *migraine* (2 participants in the EPTI100-EPTI100 group). The incidence of TEAEs that were considered *related* to IMP ranged from 3.4% to 9.2% across treatment groups.

The incidence of treatment-emergent AESIs ranged from 3.9% to 7.6% across treatment groups. Two participants had AESIs that were serious: 1 participant had an SAE of *anaphylactic reaction* and 1 participant had an SAE of *hepatic function abnormal*, both in the PBO-EPTI300 group. The SAE of *anaphylactic reaction* was considered *related* to the IMP while the SAE of *hepatic function abnormal* was considered *not related* to IMP. No AESIs led to participant withdrawal from the trial.

None of the participants died during the Extension Period. Five participants (3.9%) in the PBO-EPTI100 group, 3 participants (2.3%) in the PBO-EPTI300 group, 8 participants (3.1%) in the EPTI100-EPTI100 group, and 3 participants (1.2%) in the EPTI300-EPTI300 group had an SAE. The only SAE that occurred in >1 participant in any treatment group was *migraine* (2 participants in the EPTI100-EPTI100 group).

One pregnancy was reported during the Extension Period. The participant was in the PBO-EPTI100 group and was withdrawn from the trial due to the pregnancy. There were no complications during pregnancy and delivery. The participant gave birth to a healthy male baby.

Two participants (1.6%) in the PBO-EPTI100 group had TEAEs that led to withdrawal from the trial. The TEAEs leading to withdrawal were *papillary thyroid cancer* and *pregnancy* in 1 participant each.

A total of 3 participants had TEAEs that led to interruption or termination of the IMP infusion: 2 (1.5%) in the PBO-EPTI300 group and 1 (0.4%) in the EPTI100-EPTI100 group. There were no TEAEs leading to IMP infusion interruption or termination that occurred in >1

participant in any treatment group. Among the TEAEs that led to interruption or termination of the IMP infusion, the event of *anaphylactic reaction* (1 in the PBO-EPTI300 group) was an SAE and considered *related* to IMP.

The mean changes from Baseline in the laboratory test values, vital signs, ECG parameters (including shifts in QTcF values), and body measurement values were generally small and comparable across treatment groups, with no clinically relevant findings. The proportions of participants with post-Baseline PCS values across the variables were generally low and with no clinically relevant differences between treatment groups.

No suicidal ideation or behaviour, as assessed using the C-SSRS, occurred during the Extension Period.

Immunogenicity Results

Placebo-controlled Period

There was no difference between ADA-positive and ADA-negative participants based on the primary and first key secondary efficacy endpoints.

The assessment of the TEAEs, including TEAEs of *hypersensitivity* and *anaphylactic reactions*, in ADA-positive and ADA-negative participants did not indicate any safety signals related to ADA development.

During the Placebo-controlled Period, there was no difference between ADA-positive and ADA-negative participants regarding the analysis of changes from Baseline in MMDs or in the proportions of participants with a ≥50% reduction from Baseline in MMDs.

Extension Period

The results from the Extension Period were in line with those observed during the Placebo-controlled Period.

The assessment of the TEAEs, including TEAEs of *hypersensitivity* and *anaphylactic reactions*, in ADA-positive and ADA-negative participants did not indicate any safety signals related to ADA development.

The potential impact of ADA development on the pharmacokinetics (PK) of eptinezumab has been assessed based on data from Trials 19140A and 19140B. The presence of neutralizing anti-drug antibodies (NAbs) showed impact on clearance ($p<0.01$), and on average, clearance was 38% higher for NAb positive participants than for NAb negative participants.

Conclusions

Trial 19140A, which was conducted predominantly in participants in Asia, demonstrated efficacy for the primary and all the key secondary endpoints for both the EPTI100 and

EPTI300 groups compared to the PBO group based on results from the Placebo-controlled Period.

In the primary analysis of the primary endpoint (the mean change from Baseline in the number of MMDs [Weeks 1-12]), both doses of eptinezumab demonstrated a statistically significant difference to placebo (-2.4 days and -2.7 days in the EPTI100 and EPTI300 groups, respectively; $p<0.0001$ for both).

The results of the sensitivity analyses and the supplementary analyses of the primary endpoint were consistent with the results of the primary analyses.

In all the analyses of the key secondary endpoints, both doses of eptinezumab demonstrated ≥2-fold higher OR *versus* placebo for ≥50% reduction from Baseline in MMDs (Weeks 1-12, EPTI100: OR = 2.2; EPTI300: OR = 2.7; $p<0.0001$ for both) and ≥75% reduction from Baseline in MMDs (Weeks 1-4, EPTI100: OR = 3.9, EPTI300: OR = 4.4, $p<0.0001$ for both; Weeks 1-12, EPTI100: OR = 2.9, EPTI300: OR = 3.0, $p<0.0001$ for both). Both doses of eptinezumab also demonstrated a lower Day 1 migraine rate compared with placebo ($p<0.01$ for both).

The other secondary endpoints also showed better outcomes for both doses of eptinezumab *versus* placebo for the rate of migraines with severe pain intensity and the number of MMDs with use of acute medication. Additionally, the data for MHDs, headache responder rates, and the rate of headache with severe pain intensity showed better outcomes for both doses of eptinezumab *versus* placebo. Furthermore, improvements across PROs (PGIC and MBS) were greater for both doses of eptinezumab compared to placebo at each timepoint ($p<0.0001$).

The secondary objective of the trial was to evaluate the efficacy of eptinezumab on health-related quality of life, Health Care Resource Utilization, work productivity, and activity impairment. The results for the pharmacoeconomic endpoints (HIT-6 score, MSQ v2.1 sub-scores, EQ-5D-5L VAS score, HCRU, and WPAI:M score) consistently showed greater improvements in the EPTI100 and EPTI300 groups than in the PBO group.

The safety, tolerability, and immunogenicity profile is comparable to that observed previously with eptinezumab in participants with migraine. Eptinezumab was well tolerated with no new safety signals.