Synopsis – Trial 19140B

Trial Title Interventional, open-label, flexible-dose, long-term extension trial to evaluate safety of eptinezumab as preventive treatment in participants with migraine in Japan
Investigators 17 principal investigators at 17 sites in Japan *Signatory investigator* – [redacted]
Trial Sites 17 sites in Japan
Publications None (as of the date of this report)
Trial Period *First participant first visit* – 21 September 2021 (the date when the first *Informed Consent Form* was signed) *Last participant last visit* – 8 June 2024 (the date of the last protocol-specified contact with any participant)
Report Date 7 April 2025
This trial was conducted in compliance with *Good Clinical Practice*.

Objectives, Endpoints, and Estimands

Primary Objectives	Endpoints
• To evaluate the long-term safety and tolerability of eptinezumab	**Safety Endpoints** • Adverse events • Absolute values and changes from Baseline (Baseline of Trial 19140B) 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 anti-eptinezumab antibodies (ADAs) including NAbs • C-SSRS score

Safety Estimand:

- The estimand was the proportion of patients experiencing a TEAE among patients with CM, who have been treated with eptinezumab 100/300 mg every 12 weeks for 60 weeks, with or without the use of other preventive treatments, and regardless of infusion interruption due to other reasons than TEAE and withdrawal from trial due to other reasons than TEAE.

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 to experience at least one TEAE during 60 weeks of treatment with eptinezumab.
- The treatment condition of interest was treatment with eptinezumab 100/300 mg every 12 weeks for 60 weeks, with or without use of other preventive migraine medications.
- Intercurrent events were as follows:
  - infusion interruption due to other reasons than TEAE, which was addressed using a treatment policy strategy
  - withdrawal from trial due to other reasons than TEAE, which was handled using a while on treatment strategy
- The population level summary was the proportion of patients experiencing at least one TEAE during 60 weeks of treatment with eptinezumab.

ADA = anti-drug antibody; CM = chronic migraine; C-SSRS = Columbia-Suicide Severity Rating Scale; NAb = neutralizing antibody; TEAE = treatment emergent adverse event

Secondary Objectives	Endpoints
• To evaluate the maintenance of the therapeutic effect of eptinezumab on: – prevention of migraine – health-related quality of life	**Secondary Endpoints** • Change from Baseline in the number of MMDs (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60) • Change from Baseline in the number of MMDs (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Response: ≥50% reduction from Baseline in MMDs (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60) • Response: ≥50% reduction from Baseline in MMDs (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Change from Baseline in the HIT-6 score at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 • Change from Baseline in the EQ-5D-5L VAS score at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 • PGIC score at Weeks 12, 24, 36, 48, 60 • Change from Baseline in the MBS score at Weeks 12, 24, 36, 48, 60

Estimands for Secondary Endpoints:

- The maintenance of therapeutic effectiveness estimand was the mean change from Baseline (Baseline of Trial 19140A) in MMDs across Weeks 49-60 in patients with CM, who received double blinded treatment with placebo, eptinezumab 100 mg, or eptinezumab 300 mg for 12 weeks beforehand, now treated with eptinezumab 100 / 300 mg every 12 weeks for 60 weeks, in the hypothetical scenario where no other long-acting anti-CGRP treatment was available and where all patients managed to continue treatment, with or without the use of other preventive treatments, and regardless of infusion interruption.

The maintenance of therapeutic effectiveness estimand was described by the following attributes:

- The population of interest was patients with CM who beforehand had received double blinded treatment with placebo, eptinezumab 100 mg or 300 mg for 12 weeks.
- The endpoint to be considered was the change from Baseline in MMDs (Weeks 49-60)
- The treatment condition of interest was treatment with eptinezumab 100 / 300 mg every 12 weeks for 60 weeks (where eptinezumab 300 mg was assigned to patients not achieving at least 50% reduction in MMDs compared to Baseline when receiving eptinezumab 100 mg during Weeks 1-12), with or without the use of other preventive migraine medications except other long-acting anti-CGRPs.
- The population level summary was the mean change from Baseline in MMDs for Weeks 49-60
- Intercurrent events were:
  - use of other long-acting anti-CGRP treatments, which were handled using a hypothetical strategy
  - infusion interruption, which was handled using a treatment policy strategy
  - withdrawal from trial, which was handled using a hypothetical strategy

- Other continuous endpoints: Other continuous endpoints than change from Baseline in MMDs were handled similarly to the maintenance of therapeutic effectiveness estimand.
- 50% response endpoint: The proportion of participants with at least 50% reduction from Baseline in MMDs (Weeks 49-60) were handled similarly to the maintenance of therapeutic effectiveness estimand described above.
- Other response endpoints: Endpoints based on response variables were handled similarly to the 50% response endpoint.

ADA = anti-drug antibody; Baseline = the Baseline of Trial 19140A; CM = chronic migraine; CGRP = calcitonin gene-related peptide; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = Health-related Quality of Life; HIT-6 = Headache Impact Test-6; MBS = most bothersome symptom; MMD = monthly migraine day; PGIC = Patient Global Impression of Change; VAS = visual analogue scale

Exploratory Objectives	Endpoints
• To evaluate the long-term exposure of eptinezumab • To evaluate the maintenance of the therapeutic effect of eptinezumab on: – HCRU, and – work productivity	• Eptinezumab plasma concentrations during long-term treatment • Change from Baseline in the MSQ v2.1 sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function) at Weeks 12, 24, 36, 48, 60 • HCRU at Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 • Change from Baseline in the WPAI:M sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 • Response: ≥75% reduction from Baseline in MMDs (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60) • Response: ≥75% reduction from Baseline in MMDs (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Change from Baseline in the number of MHDs (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60) • Change from Baseline in the number of MHDs (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Response: ≥50% reduction from Baseline in MHDs (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60) • Response: ≥50% reduction from Baseline in MHDs (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Response: ≥75% reduction from Baseline in MHDs (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60) • Response: ≥75% reduction from Baseline in MHDs (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Change from Baseline in the proportion of migraine attacks with severe pain intensity (Weeks 1-12, 13-24, 25-36, 37- 48, 49-60) • Change from Baseline in the proportion of headache episodes with severe pain intensity (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Change from Baseline in monthly migraine attacks (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Change from Baseline in monthly headache episodes (Weeks 1-12, 13-24, 25-36, 37-48, 49-60) • Change from Baseline in monthly days with use of acute migraine medication (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, 33-36, 37-40, 41-44, 45-48, 49-52, 53-56, 57-60)

Baseline = the Baseline of Trial 19140A; HCRU = Healthcare Resource Utilization; MHD = monthly headache day; MMD = monthly migraine day; MSQ = Migraine-Specific Quality of Life Questionnaire Version 2.1; WPAI:M = Work Productivity and Activity Impairment Questionnaire: migraine-specific

Trial Methodology

This was an interventional, prospective, multi-site, open-label Phase III trial.

The Baseline Visit of this trial was the same as Visit 5 (Primary Outcome Visit) of the lead-in Trial 19140A. For all efficacy measures, "Baseline" corresponds to the Baseline of the lead-in Trial 19140A to ensure that all participants start from a similar Baseline level regardless of the treatment received in the lead-in Trial 19140A. Therefore, the "changes from Baseline" reported for efficacy assessments in this trial (Trial 19140B) refer to a change from Baseline of the lead-in Trial 19140A.

During the trial, the participants received the investigational medicinal product (IMP) at the Baseline Visit and once every 12 weeks (5 infusions in total) by intravenous (IV) infusions of 30 minutes (+15 minutes). Together with the infusion from the lead-in Trial 19140A, participants could receive up to 6 infusions in total. After each IMP administration 2 phone contacts were performed.

The participants who completed the trial attended a Completion Visit 60 weeks after the Baseline Visit. A Safety Follow-up Visit was performed 8 weeks after the Completion 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 scheduled 20 weeks after the last IMP Visit (date when the last dose of IMP was administered).

The participants who tested positive for anti-drug antibodies (ADAs) at the Safety Follow-up Visit were asked to provide up to two additional blood samples for immunogenicity testing at 12-week (±1 week) intervals for up to 24 weeks (up to 92 weeks in total for participants who were asked to provide extra blood samples for immunogenicity testing).

The total trial duration from the Baseline Visit to the Safety Follow-up Visit was approximately 68 weeks. The trial consisted of:

- Open-label Treatment Period - 60 weeks
- Safety Follow-up Period - 8 weeks

All participants received eptinezumab 100 mg infusion at the Baseline Visit irrespective of what dose the participant was allocated to in the lead-in Trial 19140A.

At Week 12, participants who did not have a treatment response of at least 50% reduction of monthly migraine days (MMDs) (Weeks 1-12) as compared to the Baseline of the lead-in Trial 19140A had their eptinezumab dose increased to 300 mg. This dose increase to 300 mg was only done at Week 12, and only if applicable. The investigator was informed about the 50% responder status based on information recorded in the participant's eDiary, and automatically calculated relative to the Baseline of the lead-in Trial 19140A. The investigator acknowledged and recorded the change in dose in the electronic case report form (eCRF) at Week 12.

After Week 12, all participants continued receiving the same eptinezumab dose as at Week 12 for the remainder of the trial. The exception was the participants on eptinezumab 300 mg who had tolerability issues (who were allowed to switch to eptinezumab 100 mg once between Weeks 16 to 48 [inclusive] and then remained on the 100 mg dose for the remainder of the trial).

The participants completed a daily eDiary from the Baseline Visit until the Completion/Withdrawal Visit. The eDiary data from the 28 days prior to Baseline Visit of the lead-in Trial 19140A was used for generating Baseline values for eDiary-based endpoints.

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

Number of Participants Planned

A total of 154 participants were planned for enrolment, with the aim to have 100 participants for evaluating 12 months exposure safety.

Main Selection Criteria

The participants had to be outpatients with a diagnosis of chronic migraine (CM) according to the International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 guidelines and a history of migraine onset at least 12 months prior to the Screening Visit of the lead-in Trial 19140A who:

- had completed the Primary Outcome Visit (Visit 5) of the lead-in Trial 19140A immediately prior to enrolment into this trial
- were indicated for 60-week preventive treatment of CM with eptinezumab according to the clinical opinion of the investigator

The participants had to have completed the placebo-controlled period of the lead-in Trial 19140A. At entry into the lead-in trial, the participants were enrolled 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 eDiary during the Screening Period
  - migraine occurring on ≥8 days and headache occurring on ≥15 to ≤26 days
  - had demonstrated compliance with the Headache eDiary by entry of data for at least 24 of the 28 days following the Screening Visit
- were aged ≥18 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 (CGRP) pathway for preventive treatment of migraine were excluded from the lead-in Trial 19140A. The individuals with concurrent

medication overuse headache (MOH) diagnosis at entry into the lead-in Trial 19140A were allowed to continue in this trial.

Investigational Medicinal Product, Doses, and Modes of Administration

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

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

Participants allocated to the 300 mg eptinezumab received 3x 100 mg concentrate for solution for infusion 100 mg/mL of 0.9% normal saline, IV.

Duration of Treatment

The total trial duration of the treatment period was 60 weeks.

Statistical Methodology

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

- *all-participants-enrolled set* (APES) – all participants who have completed the placebo-controlled period of the lead-in Trial 19140A and were enrolled into Trial 19140B
- *all-participants-treated set* (APTS) – all participants in the APES who received IMP in Trial 19140B
- *full-analysis set* (FAS) – all participants in the APTS who had a valid Baseline assessment of MMDs (based on the eDiary data from the first 28 days of the Screening Period of Trial 19140A) and at least one valid post-Baseline assessment of MMDs in Trial 19140B

Unless otherwise specified, all outputs are based on the APTS, except for the efficacy analyses and eDiary Compliance, which are based on FAS. All confidence intervals (CIs) were two-sided 95% CIs.

The primary endpoints are safety endpoints. There are secondary efficacy endpoints and no primary efficacy endpoints.

Analysis of Safety Endpoints

The proportion of participants experiencing at least one treatment-emergent adverse event (TEAE) is presented descriptively. In addition to the descriptive statistic, a CI based on normality assumptions is presented.

Analysis of Secondary Endpoints

Change from Baseline in MMDs Weeks 49-60 was analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The analysis was performed using all available monthly scores derived as specified in the statistical

analysis plan (SAP). Below, the term "month" refers to 4-week periods. The model included the following fixed effects: month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24, Weeks 25-28, Weeks 29-32, Weeks 33-36, Weeks 37-40, Weeks 41-44, Weeks 45-48, Weeks 49-52, Weeks 53-56, Weeks 57-60) as a factor, Baseline MMDs as continuous covariate and Baseline score-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.

Other continuous secondary and exploratory efficacy endpoints were analyzed using the same methodology as described for the maintenance of therapeutic effectiveness estimand above, with the appropriate Baseline values and the appropriate contrast statement. For endpoints regarding response the number and percentages of responders were summarized by 4-weeks intervals and by 12-weeks intervals.

Participant Disposition and Analysis Sets

Participant disposition is summarized below:

	EPTI 100/300mg	
	n	(%)
Participants enrolled	160	
Participants treated (APTS)	159	
Participants completed	141	(88.7)
Participants withdrawn	18	(11.3)
Primary reason for withdrawal		
Adverse events	6	(3.8)
Lack of efficacy	3	(1.9)
Withdrawal of consent	9	(5.7)
Analysis sets:		
APES	160	
APTS	159	
FAS	158	(99.4)

APES = all-participants-enrolled set; APTS = all-participants-treated set;
EPTI = eptinezumab; FAS = full-analysis set

Demographics and Baseline Characteristics of the Trial Population

The mean age of the participants was 42 years and the vast majority of them were women (87%). All participants were from Japan. Overall, demographics were comparable between participants according to the prior treatment groups in Trial 19140A.

Overall, the mean height, weight, and body mass index (BMI) were respectively 160 cm, 59 kg, and 23 kg/m^2. Baseline height, weight, and BMI were comparable between participants according to the prior treatment groups in Trial 19140A.

The mean age at migraine diagnosis was 39 years and the mean duration of migraine (time since diagnosis) at Baseline was 3.5 years. The vast majority of the participants (84%) did not suffer from aura. In the majority of participants with aura, aura symptoms were visual and

none had aura without headaches. A total of 35% of the participants had MOH concomitantly to CM.

At Baseline (Baseline of Trial 19140A), based on prospectively collected data (eDiary), the mean number of MMDs was 17 days and the mean number of monthly headache days (MHDs) was 20 days.

At Baseline, the most common most bothersome symptom (MBS) reported was *pain with activity* (36%), followed by *nausea* (18%) and *fatigue* (15%). The mean Headache Impact Test-6 (HIT-6) total score was 64, and HIT-6 Life Impact Category was *severe* for the majority of the participants (84%). The mean Baseline Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1) sub-scores were 52 points for *MSQ Role Function Restrictive*; 71 points *MSQ Role Function Preventive*; and 63 points for *MSQ Emotional Function* (each MSQ v2.1 sub-score was out of 100 points). The mean Health-related Quality of Life (EQ-5D-5L) Visual Analogue Scale (VAS) score was 71 out of 100. The mean Work Productivity and Activity Impairment (WPAI) sub-scores ranged from 50 to 57, except for absenteeism, for which the mean score was 3.8. The participants were going to work despite the burden due to migraine. The majority of the participants (60%) had not visited a doctor or general practitioner during the 4 weeks prior to the Baseline Visit of Trial 19140A.

Exposure

The infusions were completed as planned in all participants.

Among the 159 participants treated, 146 had an exposure of 1-year (defined as receiving 4 consecutive infusions with eptinezumab and having data for at least 365 days across Trials 19140A and 19140B).

A total of 123 participants (77%) received eptinezumab 300 mg at least once in the trial. Two participants had a dose reduction from eptinezumab 300 mg to eptinezumab 100 mg (one due to non-serious adverse events at Week 24 and one due to treatment allocation mistake at Week 36); both completed the trial.

Efficacy/Pharmacoeconomic Summary

Based on the maintenance of therapeutic effectiveness estimand, the mean change from Baseline (Baseline of Trial 19140A) in MMDs across Weeks 49-60 was -5.4 days. The mean change from Baseline in MMDs was -4.4 days across Weeks 1-12. This initial symptom reduction was maintained throughout the trial (-5.4 days across Weeks 49-60).

The proportion of participants with a ≥50% reduction from Baseline in MMDs was 29% across Weeks 1-12. This initial symptom reduction was maintained throughout the trial (36% across Weeks 49-60).

The results from the sensitivity analyses were in line with the analyses described above.

The mean Patient Global Impression of Change (PGIC) and MBS scores showed improvements at all visits. Initial symptom reduction was maintained throughout the trial for the mean PGIC score from Week 12 (3.0) to Week 60 (2.5) and for the mean MBS score from Week 12 (3.1) to Week 60 (2.6), that is from *minimally improved* to *much improved* for both PGIC and MBS.

At all intervals assessed, there were decreases, corresponding to an improvement, from Baseline in HIT-6 total score. Initial symptom reduction was maintained throughout the trial for the mean decrease in HIT-6 total score from Week 4 (-7.2) to Week 60 (-8.9). There were no consistent mean changes from Baseline in EQ-5D-5L VAS Score, ranging from 1.0 at Week 4 to 2.9 at Week 60.

Results for the exploratory endpoints were in line with those for the secondary endpoints, showing initial symptom reduction within the first 12 weeks that was maintained throughout the trial including the number of MHDs, the monthly number of migraine attacks and headache episodes, the rate of migraines and headaches with severe pain intensity, the number of MMDs with use of acute medication, ≥75% response in MMDs, ≥50% response in MHDs, ≥75% response in MHDs, MSQ v2.1, Health Care Resource Utilization (HCRU), and in most WPAI:M subscores.

The results were generally comparable between the prior treatment groups (lead-in Trial 19140A).

Safety Results

Based on the safety estimand, the proportion of participants with at least one TEAE was 84% (95% CI: 78%; 89%).

The adverse event incidence is summarized below:

	EPTI 100/300mg	
	n	(%)
Number of Participants	159	
Participants with TEAEs	133	(83.6)
Participants with SAEs	5	(3.1)
Participants with TEAEs leading to withdrawal	7	(4.4)
Participants with TEAEs leading to infusion interruption or termination	8	(5.0)
Deaths	0	(0.0)
Total number of TEAEs	377	
Total number of SAEs	5	

EPTI = eptinezumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event

The incidences of serious adverse events (SAEs) (3.1%), TEAEs leading to withdrawal (4.4%), and TEAEs leading to infusion interruption or termination (5.0%) were low. None of the trial participants died.

The SOCs with the highest incidences of TEAEs (≥10% of participants) were *infections and infestations* (49%), *gastrointestinal disorders* (18%), *general disorders and administration site conditions* (15%), *musculoskeletal and connective tissue disorders* (14%), *nervous system disorders* (13%), *respiratory, thoracic and mediastinal disorders* (11%), and *injury, poisoning and procedural complications* (10%).

The most common TEAEs (≥5%) on preferred term level were *COVID-19* (25%), *nasopharyngitis* (11%), *cystitis* (5.0%), and *migraine* (5.0%).

Preferred Term (MedDRA Version 27.0)	EPTI 100/300mg n	(%)
Participants treated	159	
COVID-19	40	(25.2)
Nasopharyngitis	18	(11.3)
Cystitis	8	(5.0)
Migraine	8	(5.0)

COVID-19 = Coronavirus disease 2019; EPTI = eptinezumab; MedDRA = Medical Dictionary for Regulatory Activities

For the majority of participants with TEAEs, the TEAEs were *mild* or *moderate*. There were 2.5% of participants with *severe* TEAEs.

The incidence of TEAEs considered related to the IMP was 22%, with the most common being *malaise* (2.5%).

The overall incidence of treatment-emergent adverse events of special interest (AESIs) was 21%. All of the events were non-serious and *mild* or *moderate*. AESIs of *hypersensitivity and anaphylactic reactions* were most frequently reported (11%), followed by *events potentially associated with the IMP infusion* (5.0%). None of the participants had adverse events of *suicidal ideation and behaviour* or *seizures.*

None of the treatment-emergent SAEs were reported by >1 participant.

The only TEAE leading to withdrawal reported by >1 participant was *pregnancy* (2 participants [1.3%]).

TEAEs leading to interruption of the IMP infusion reported by >1 participant were *puncture site pain* (3 participants [1.9%]), and *infusion site extravasation* and *infusion site pain* (2 participants [1.3%] each). None of the TEAEs led to termination of the IMP.

The mean changes from Baseline and the proportion of participants with post-Baseline potentially clinically significant values in the laboratory test values, vital signs, electrocardiogram (ECG) parameter values, and body measurements were generally low with no clinically relevant findings. None of the participants met the criteria for Hy's Law. No participants had suicidal ideation or behaviour based upon the Columbia-Suicide Severity Rating Scale (C-SSRS).

No new safety signals were seen in the trial and the safety and tolerability profile is consistent with what was previously seen in clinical trials with eptinezumab.

Immunogenicity Results

The overall ADA incidence was 20%. The percentages of ADA positive samples declined after Week 24 (17% at Week 24 to 7.7% at Week 60). At Week 92 (ADA Follow-up at Week 92 for participants with positive ADA samples at Safety Follow-up), none of the participants were ADA-positive. Of the participants who were ADA-positive, 19% were NAb-positive. The ADA prevalence was 21%.

There was no consistent difference between ADA-positive and ADA-negative participants regarding the proportion of participants achieving at least a 50% reduction in MMDs.

The proportion of ADA-positive and ADA-negative participants that reported TEAEs was similar (84% each). Two out of 32 (6.3%) ADA-positive participants and 15 out of 127 (12%) ADA-negative participants had TEAEs of *hypersensitivity and anaphylactic reactions.*

Overall, the assessment of TEAEs, including TEAEs of *hypersensitivity and anaphylactic reactions* by ADA status, did not indicate safety signals related to ADA development.

There was no evidence of impact of ADA development on efficacy or safety.

Conclusions

The primary objective of this trial was to evaluate the long-term safety and tolerability of eptinezumab in the Japanese population. Based on the safety estimand, the proportion of participants with at least one TEAE was 84% (95% CI: 78%; 89%).

The incidences of SAEs (3.1%), TEAEs leading to withdrawal (4.4%), and TEAEs leading to infusion interruption or termination (5.0%) were low. No deaths were reported. The most common TEAEs were in line with those observed in previous eptinezumab trials. No clinically relevant findings were identified from laboratory test values, vital signs, ECG parameters, body measurement values, or the C-SSRS. Overall, there were no safety signals related to long-term use of eptinezumab.

The overall ADA incidence was 20%, which is within the range of that in previous trials. The percentage of ADA positive samples declined after Week 24, which is in line with observations in previous eptinezumab trials. At Week 92 (ADA Follow-up Week 92), none of the participants were ADA-positive. There was no evidence of impact of ADA development on efficacy measures or safety.

The secondary objective was to evaluate the maintenance of the therapeutic effect of eptinezumab on the prevention of migraine and on health-related quality of life. Based on the maintenance of therapeutic effectiveness estimand, the mean change from Baseline (Baseline of Trial 19140A) in MMDs across Weeks 49-60 was -5.4 days. Consistent with the results

based on the maintenance of therapeutic effectiveness estimand, there were decreases in MMDs from Baseline for all other intervals assessed. Initial symptom reduction was observed within the first 12 weeks and maintained throughout the trial for the secondary endpoints ≥50% reduction from Baseline in MMDs, PGIC, MBS, WPAI (*presenteeism*, a*ctivity impairment*, and *work productivity*), and HIT-6 scores, but no consistent trend was observed for EQ-5D-5L VAS score.

Results for the exploratory endpoints were in line with those for the secondary endpoints, showing initial symptom reduction within the first 12 weeks that was maintained throughout the trial.

Overall, eptinezumab was well tolerated after long-term treatment up to 60 weeks. The long-term safety and tolerability profile in this trial for Japanese participants was comparable to that observed previously with eptinezumab in participants with migraine. Symptom reduction was achieved and maintained throughout the trial.