Synopsis – Study 19139A

Study Title Interventional, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for the preventive treatment of migraine in patients with a dual diagnosis of migraine and medication overuse headache	
Investigators 40 principal investigators at 40 sites in Asia and Europe *Signatory investigator* – [redacted]	
Study Sites 40 sites – 26 in China, 2 in Georgia, 3 in Republic of Korea, 6 in Spain, 3 in Taiwan	
Publications None (as of the date of this report)	
Study Period *First patient first visit* – 17 February 2021 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 30 September 2022 (the date of the last protocol-specified contact with any patient)	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • to evaluate the efficacy of eptinezumab for the prevention of migraine and medication overuse headache (MOH)	• Primary endpoint: – change from Baseline in *monthly migraine days* (MMDs) (Weeks 1-12) • Key secondary endpoints: – change from Baseline in MMDs with use of acute medication (Weeks 1-12) – response: ≥50% reduction from Baseline in MMDs (Weeks 1-12) – migraine on the day after dosing (Day 1) – response: ≥75% reduction from Baseline in MMDs (Weeks 1-4) – change from Baseline in *monthly headache days* (MHDs) (Weeks 1-12) – response: ≥75% reduction from Baseline in MMDs (Weeks 1-12) • Secondary endpoints: – response: ≥75% reduction from Baseline in MHDs (Weeks 1-12) – response: ≥75% reduction from Baseline in MHDs (Weeks 1-4) – change from Baseline in MHDs with use of acute medication (Weeks 1-12) – change from Baseline in the proportion of *migraine attacks* with severe pain intensity (Weeks 1-12) – change from Baseline in the proportion of *headache episodes* with severe pain intensity (Weeks 1-12) – Patient Global Impression of Change (PGIC) score at Week 12 – change score at Week 12 in most bothersome symptom (MBS) (as reported at Screening)

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Primary Objective (continued)	• Exploratory endpoints: – [redacted] – [redacted] – [redacted] – [redacted] – [redacted] – [redacted] – [redacted] – [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
Secondary Objective • 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 Headache Impact Test (HIT-6) total score • response: ≥5-point reduction from Baseline to Week 12 in the HIT-6 total score • change from Baseline to Week 12 in the Migraine-Specific Quality of Life (MSQ) version 2.1 subscores (*Role Function-Restrictive*, *Role Function-Preventive*, *Emotional Function*) • change from Baseline to Week 12 in the Health-Related Quality of Life (EQ-5D-5L) visual analogue scale (VAS) score • Health Care Resource Utilization (HCRU) at Baseline and at Week 12 • change from Baseline to Week 12 in the Work Productivity and Activity Impairment (WPAI) questionnaire subscores (*Absenteeism*, *Presenteeism*, *Work Productivity Loss*, *Activity Impairment*)

Objectives and Endpoints (continued)

Objectives	Endpoints
Safety Objective • to evaluate the safety and tolerability of eptinezumab	**Safety Endpoints** • adverse events • absolute values and changes from Baseline in clinical safety laboratory test values, vital signs, weight, and electrocardiogram (ECG) parameter values • potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • development of specific anti-eptinezumab antibodies (ADA) including neutralizing antibodies (NAbs) • Columbia-Suicide Severity Rating Scale (C-SSRS) score

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled study.
- The study consisted of:
  - Screening Period – 28- to 30-day period from screening to randomization
  - Placebo-controlled Period – 12-week double-blind treatment period with placebo or eptinezumab 100 mg
  - Open-label Period – 12-week open-label treatment period with eptinezumab 100 mg
- The Safety Follow-up Visit was conducted 20 weeks after the last investigational medicinal product (IMP) administration.
- Placebo-controlled Period: The patients were randomized 1:1 to 12 weeks of double-blind treatment with placebo or eptinezumab 100 mg; the corresponding treatment groups are referred to as PBO and EPTI100. Randomization was stratified by site and Baseline MHDs (<20 MHDs/≥20 MHDs). The patients received IMP by intravenous (IV) infusion over 30 minutes (up to 45 minutes), at the Baseline Visit.
- Open-label Period: The patients entered the Open-label Period, after completing the Placebo-controlled Period. All the patients were dosed with eptinezumab 100 mg at the Week 12 Visit; the treatment groups are referred to as PBO-EPTI100 and EPTI100-EPTI100 for the patients treated with placebo and eptinezumab 100 mg, respectively, in the Placebo-controlled Period. The total EPTI100 group comprises the PBO-EPTI100 and EPTI100-EPTI100 groups.
- Efficacy and pharmacoeconomic data were collected in the Placebo-controlled Period only. Safety assessments were performed throughout the study.

Number of Patients Planned

182 patients were planned for randomization, with 91 patients in each treatment group.

Diagnosis and Main Selection Criteria

Outpatients with a dual diagnosis of migraine and MOH according to *International Headache Society International Classification of Headache Disorders, 3rd Edition*, criteria, who:

- had a history of migraine for ≥12 months prior to the Screening Visit
- had an onset of migraine at ≤50 years of age
- had ≥8 MMDs each month in the 3 months prior to the Screening Visit
- had ≥15 MHDs each month in the 3 months prior to the Screening Visit and had a regular overuse of one or more drugs that can be taken for acute and/or symptomatic treatment of headache for >3 months
- had ≥15 to ≤26 *headache days*, of which ≥8 days were assessed as *migraine days* during the Screening Period, based on prospectively collected information in the eDiary
- had MO for acute and/or symptomatic treatment of headache during the Screening Period, based on prospectively collected information in the eDiary
- were ≥18 (in Taiwan: ≥20) and ≤75 years of age

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

Eptinezumab – 100 mg; concentrate for solution for infusion, 100 mg/mL added to 100 mL of 0.9% saline solution (prepared on site), IV; batch No. APSG01

Control Product, Dose and Mode of Administration

Placebo – 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:
  - *all-patients-randomized set* (APRS) – all randomized patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who received an infusion of the double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid Baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12
  - *all-patients-treated-open-label set* (APTS-OL) – all patients in the APRS who received an infusion of the open-label IMP in the Open-label Period
  - *all-patients-treated-follow-up set* (APTS-FU) – all patients in the APTS who were not in the APTS-OL and who had data collected from the Safety Follow-up Visit.
- Unless otherwise specified, the efficacy and pharmacoeconomic analyses and data presentations are based on the FAS; all the safety analyses and data presentations are based on the APTS for the Placebo-controlled Period, the APTS-OL for the Open-label Period, and the APTS-FU for the patients who were not in the APTS-OL and who had data from the Safety Follow-up Visit.
- The change from Baseline in MMDs (Weeks 1-12) was analysed using a restricted maximum likelihood-based mixed model for repeated measures (MMRM). The analysis was performed using all available monthly (4-week period: Weeks 1-4, Weeks 5-8, Weeks 9-12) change from Baseline scores for the first 12 weeks of the study. The analysis was performed on MMDs by month, with Baseline MMDs as a continuous covariate, and treatment, stratum (MHDs at Baseline: <20 MHDs/≥20 MHDs), month, and region as fixed factors. In addition, the model included treatment-by-month interaction; Baseline MMDs-by-month interaction; and stratum-by-month interaction. An unstructured variance structure was used to model the within-patient 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 3 4-week intervals, and the treatment effect was calculated from the least squares estimates from the MMRM for the month × treatment interaction via a contrast (1/3, 1/3, 1/3, -1/3, -1/3, -1/3) comparing the effect of eptinezumab to the effect of placebo across Weeks 1-12.
- The estimand for the primary endpoint was the mean difference in the change from Baseline in MMDs (Weeks 1-12) in patients with a dual diagnosis of migraine and MOH treated with eptinezumab and placebo, regardless of use of preventive migraine treatment and regardless of interruption or termination of the infusion.
  - The intercurrent events addressed were:
    - use of preventive migraine medication
    - interruption/termination of infusions
  - The attributes for the estimand included:
    - *treatment condition* – comparing eptinezumab 100 mg to placebo with or without use of preventive migraine medication
    - *population* – as defined in the inclusion and exclusion criteria
    - *endpoint* – the change from Baseline in MMDs (Weeks 1-12)
    - *population-level summary* – the least squares mean difference between eptinezumab and placebo for the primary endpoint
    - *other intercurrent event* – interruption/termination of infusions

Statistical Methodology (continued)

- A sensitivity analysis using placebo multiple imputation (pMI) was performed for the primary analysis.
- The key secondary endpoints related to ≥50% and ≥75% reduction from Baseline in MMDs were analysed using logistic regression. The model included Baseline MMDs as a continuous covariate and treatment and stratum (MHDs at Baseline: <20 MHDs/≥20 MHDs) as factors.
- The key secondary endpoint, change from Baseline in MMDs with use of acute medication (Weeks 1-12) defined as 4-week intervals (Weeks 1-4, Weeks 5-8, Weeks 9-12), was analysed using the same MMRM as for the primary endpoint. In the model, the Baseline MMDs were replaced with Baseline MMDs with use of acute medication.
- Migraine on the day after dosing (Day 1) was analysed using an extended Cochran-Mantel-Haenszel test, adjusting for the stratum (MHDs at Baseline: <20 MHDs/≥20 MHDs).
- Sensitivity analyses (pMI for continuous endpoints; non-response for endpoints related to ≥50% and ≥75% reduction from Baseline in MMDs; both response and non-response for migraine on the day after dosing) for each key secondary endpoint were performed.
- The testing strategy was planned as a sequence of tests testing one endpoint at a time. If the results of the first step were statistically significant, the formal testing continued with the next step and so on, ensuring protection of the type 1 error. A significance level of 0.05 was used. The testing started with the primary endpoint (change from Baseline in MMDs [Weeks 1-12]) and was to be followed by the key secondary endpoints in the following order: change from Baseline in MMDs with use of acute medication (Weeks 1-12), ≥50% reduction from Baseline in MMDs (Weeks 1-12), migraine on the day after dosing (Day 1), ≥75% reduction from Baseline in MMDs (Weeks 1-4), change from baseline in MHDs (Weeks 1-12), and ≥75% reduction from baseline in MMDs (Weeks 1-12).
- In a prior study of eptinezumab, the subgroup of patients with MOH showed an advantage of 3.0 MMDs for the eptinezumab 100 mg dose compared to placebo, with a standard deviation of 6.0. Assuming the same effect size, 86 patients per treatment provides a power of 90% for the primary endpoint using a 5% significance level. To account for 5% of randomized patients not contributing to the primary endpoint, 91 patients randomized per treatment group, or 182 randomized patients in total, should provide a power of 90% to detect an effect size similar to the one for the MOH subgroup in the prior study.

Patient Disposition and Analysis Sets

- 332 patients were screened
- Patient disposition in the Placebo-controlled Period is summarized below:

	PBO		EPTI100		Total	
	n	(%)	n	(%)	n	(%)
Patients randomized	100		93		193	
Patients treated (APTS)	100	(100)	93	(100)	193	(100)
Patients completed	83	(83.0)	81	(87.1)	164	(85.0)
Patients withdrawn	17	(17.0)	12	(12.9)	29	(15.0)
Primary reason for withdrawal:						
Adverse event(s)	1	(1.0)	2	(2.2)	3	(1.6)
Withdrawal of consent	2	(2.0)	0		2	(1.0)
Other	14	(14.0)	10	(10.8)	24	(12.4)
COVID-19	11		9		20	
Analysis sets:						
APRS	100		93		193	
APTS	100		93		193	
FAS	100		90		190	

Patient Disposition and Analysis Sets (continued)

- Patient disposition in the Open-label Period is summarized below:

	PBO-EPTI100		EPTI100-EPTI100		Total	
	n	(%)	n	(%)	n	(%)
Patients treated	81		81		162	
Patients completed	71	(87.7)	66	(81.5)	137	(84.6)
Patients withdrawn	10	(12.3)	15	(18.5)	25	(15.4)
Primary reason for withdrawal:						
Adverse event(s)	1	(1.2)	1	(1.2)	2	(1.2)
Lack of efficacy	0		3	(3.7)	3	(1.9)
Withdrawal of consent	2	(2.5)	3	(3.7)	5	(3.1)
Lost to follow-up	0		2	(2.5)	2	(1.2)
Other	7	(8.6)	6	(7.4)	13	(8.0)
COVID-19	3		2		5	
Analysis sets:						
APTS-OL	81		81		162	

Demographics and Baseline Characteristics of the Study Population

- The demographics were comparable across treatment groups. The mean age of the patients was 44 years. The majority of the patients were women (78%), >35 years old (75%), and Asian (82%) (primarily Chinese).
- Overall, the demographics at Baseline for the patients who continued in the Open-label Period were similar to those for all the patients.
- The treatment groups were comparable with respect to migraine history. The mean time since first migraine diagnosis was 8 years, and the mean age at first diagnosis of migraine was 36 years.
- Approximately 13% of the patients had a diagnosis of migraine with aura and 3% of the patients had aura symptoms without headache.
- At Baseline, the patients had a mean of 20 MMDs.
- The mean HIT-6 score was 64 points (a score ≥60 points indicates *severe* impact of headache on the patients' ability to function normally in daily life). The mean MSQ subscores ranged from 41 to 61 points and indicate reduced quality of life; the mean EQ-5D-5L VAS score was 75 points and reflects the impact of migraine on overall well-being. The mean WPAI subscores ranged from 7.9 to 62 points; a score of 7 points indicates that, in the 7 days prior to Baseline, migraine episodes had had an impact on the patients' work productivity and impaired their ability to complete normal daily activities.

Efficacy and Pharmacoeconomic Results

- The mean change from Baseline in MMDs (Weeks 1-12) was -5.9 and -7.2 days for placebo and eptinezumab 100 mg, respectively. In the primary analysis of the primary endpoint (the mean change from Baseline in MMDs [Weeks 1-12]), eptinezumab 100 mg did not demonstrate a statistically significant difference to placebo (-1.2 days; p = 0.15). The testing strategy stopped at this step. The results of the sensitivity analysis of the primary endpoint were consistent with the results of the primary analysis, and also numerically in favour of eptinezumab.
- The results of the analysis of the key secondary endpoints and of the secondary and exploratory endpoints based on the eDiary-derived variables including response were also consistent with those of the primary efficacy analysis. For the majority of the endpoints, the improvements were consistently numerically in favour of eptinezumab 100 mg.
- The results of the analyses of the secondary endpoints based on the PGIC, MBS, MSQ, and HIT-6 were consistent with the results of the primary analysis. For all of the endpoints, the improvements were consistently numerically in favour of eptinezumab 100 mg.
- The results of the analyses of the pharmacoeconomic endpoints based on the WPAI and EQ-5D-5L were consistent with the results of the primary analysis. For all of the endpoints, the improvements were consistently numerically in favour of eptinezumab 100 mg.
- The results related to HCRU indicated that, overall, the patients' use of health care resources were numerically lower during the study for the patients treated with eptinezumab 100 mg than for the patients treated with placebo.

Safety Results

Placebo-controlled Period

- The adverse event incidence is summarized below:

	PBO		EPTI100	
	n	(%)	n	(%)
Patients treated	100		93	
Patients who died	0		0	
Patients with treatment-emergent serious adverse events (SAEs)	0		2	(2.2)
Patients with treatment-emergent adverse events (TEAEs)	34	(34.0)	38	(40.9)
Patients with TEAEs leading to withdrawal	1	(1.0)	2	(2.2)
Total number of treatment-emergent SAEs	0		2	
Total number of TEAEs	59		74	
Total number of TEAEs leading to withdrawal	1		2	

- The overall incidence of TEAEs was approximately 37%, with a similar distribution across treatment groups. The incidences of SAEs and TEAEs leading to withdrawal were low.
- The system organ classes (SOCs) with the highest incidence of TEAEs (>10% in either treatment group) were *infections and infestations* (12% and 9.7% in the PBO and EPTI100 group, respectively) and *gastrointestinal disorders* (6.0% and 11% in the PBO and EPTI100 group, respectively).

Safety Results (continued)

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

Preferred Term (MedDRA Version 25.0)	PBO n	PBO (%)	EPTI100 n	EPTI100 (%)
Patients treated	100		93	
Upper Respiratory Tract Infection	2	(2.0)	3	(3.2)
Dermatitis Atopic	0		2	(2.2)
Diarrhoea	1	(1.0)	2	(2.2)
Dizziness	2	(2.0)	2	(2.2)
Glycosylated Haemoglobin Increased	1	(1.0)	2	(2.2)
Muscle Spasms	0		2	(2.2)
Nasopharyngitis	0		2	(2.2)
Nausea	2	(2.0)	2	(2.2)
Protein Urine Present	0		2	(2.2)
Urinary Tract Infection	1	(1.0)	2	(2.2)
Influenza Line Illness	2	(2.0)	1	(1.1)
Fatigue	4	(4.0)	0	
Urinary Tract Infection Bacterial	4	(4.0)	0	

- The most common TEAEs were *fatigue* and *urinary tract infection bacterial*, both only in the PBO group and each with an incidence of 4%. For all the other TEAEs, the incidences were <3% in either treatment group. For all of the patients with TEAEs, the TEAEs were *mild* or *moderate*.
- The incidence of treatment-emergent adverse events of special interest (AESIs) was low; the highest incidence of AESIs was related to *hypersensitivity and anaphylactic reactions*, where 5.4% (5 patients, all in the EPTI100 group) had treatment-emergent AESIs. The only AESI that occurred in >1 patient was *dermatitis atopic* (2 patients, both in the EPTI100 group). The only treatment-emergent AESI that was *serious* was 1 SAE of *acute myocardial infarction* (reported as a acute myocardial infarction with ST elevation; the diagnosis was confirmed) in the EPTI100 group in a 65-year-old woman with risk factors of high body mass index (BMI) and a long history of heavy smoking. The SAE was considered *related* to the IMP and led to withdrawal from the study; the patient recovered from the event. One patient in the PBO group had s*uicidal ideation*; the event was considered *not related* to the IMP and led to withdrawal from the study. One patient in the EPTI100 group had *drug eruption*; the event was considered *related* to the IMP and led to withdrawal from the study. All other AESIs were non-serious, reported in single patients, and did not lead to withdrawal from the study.
- None of the patients died. Two patients in the EPTI100 group had a treatment-emergent SAE (*acute myocardial infarction* and *rib fracture*); of the 2 SAEs, only *acute myocardial infarction* was considered *related* to the IMP.
- No TEAEs led to IMP infusion interruption or termination.
- Three patients had an adverse event that led to withdrawal from the study: 1 in the PBO group (s*uicidal ideation*) and 2 in the EPTI100 group (*acute myocardial infarction* and *drug eruption*); all the TEAEs leading to withdrawal were AESIs.
- The mean changes from Baseline in the laboratory test values, vital signs, ECG parameter values (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 patients with post-Baseline PCS values were generally low and there were no clinically relevant differences between treatment groups. Evaluation of liver enzymes did not show any clinically relevant findings. No patients met the criteria for Hy's law.
- One patient in the PBO group reported *active suicidal ideation with specific plan and intent*, 1 patient in the EPTI100 group reported *wish to be dead,* and 1 patient in the EPTI100 group reported *non-suicidal self-injurious behaviour* as assessed using the C-SSRS.

Safety Results (continued)

Open-label Period

- The adverse event incidence is summarized below:

	PBO-EPTI100		EPTI100-EPTI100	
	n	(%)	n	(%)
Patients treated	81		81	
Patients who died	0		0	
Patients with SAEs	0		4	(4.9)
Patients with TEAEs	38	(46.9)	34	(42.0)
Patients with TEAEs leading to withdrawal	1	(1.2)	1	(1.2)
Total number of treatment-emergent SAEs	0		7	
Total number of TEAEs	71		74	
Total number of TEAEs leading to withdrawal	1		1	

- The overall incidence of TEAEs was approximately 44%. The incidences of SAEs and TEAEs leading to withdrawal were low.
- The SOC with the highest incidence of TEAEs (>10% in the total EPTI100 group) was *infections and infestations* (21%)
- TEAEs with an incidence ≥2% in either treatment group (PBO-EPTI100 or EPTI100-EPTI100) are summarized below:

Preferred Term	PBO-EPTI100		EPTI100-EPTI100		Total EPTI100	
(MedDRA Version 25.0)	n	(%)	n	(%)	n	(%)
Patients treated	81		81		162	
Migraine	1	(1.2)	5	(6.2)	6	(3.7)
Covid-19	3	(3.7)	3	(3.7)	6	(3.7)
Pyrexia	0		3	(3.7)	3	(1.9)
Urinary Tract Infection	0		3	(3.7)	3	(1.9)
Bronchitis	1	(1.2)	2	(2.5)	3	(1.9)
Glucose Tolerance Impaired	0		2	(2.5)	2	(1.2)
Headache	0		2	(2.5)	2	(1.2)
Myalgia	1	(1.2)	2	(2.5)	3	(1.9)
Pharyngotonsillitis	0		2	(2.5)	2	(1.2)
Dizziness	3	(3.7)	1	(1.2)	4	(2.5)
Abdominal Pain Upper	2	(2.5)	0		2	(1.2)
Diarrhoea	2	(2.5)	0		2	(1.2)
Fatigue	2	(2.5)	0		2	(1.2)
Hyperlipidaemia	3	(3.7)	0		3	(1.9)
Proteinuria	2	(2.5)	0		2	(1.2)
Upper Respiratory Tract Infection	11	(13.6)	0		11	(6.8)

- In the Total EPTI100 group, the most common TEAE was *upper respiratory tract infection*, which occurred in 6.8% (11 patients, all in the PBO-EPTI100 group) of the patients; the incidences of both *migraine* and *COVID-19* were 3.7% (6 patients). For all the other TEAEs in the Total EPTI100 group, the incidences were <3%. For the vast majority of the patients with TEAEs, the TEAEs were *mild* or *moderate*.
- The incidence of AESIs was low; the highest incidence of AESIs was related to *hepatic events*, where 3.7% (6 patients) had treatment-emergent AESIs. None of the AESIs were *serious* or occurred in >1 patient. One patient in the EPTI100-EPTI100 group had *hypersensitivity*; the event was considered *related* to the IMP and led to withdrawal from the study.

Safety Results (continued)

- None of the patients died. Four patients, all in the EPTI100-EPTI100 group, had treatment-emergent SAEs. None of the SAEs occurred in >1 patient. All the SAEs were considered *not related* to the IMP. Two patients had an adverse event that led to withdrawal from the study: 1 in the PBO-EPTI100 group (*pregnancy*) and 1 in the EPTI100-EPTI100 group (*hypersensitivity*).
- No TEAEs led to IMP infusion interruption or termination.
- One patient in the PBO-EPTI100 group became pregnant. The patient had an elective abortion.
- The mean changes from Baseline in the laboratory test values, vital signs, ECG parameter values (including shifts in *QTcF* values), and body measurement values were generally small, with no clinically relevant findings. The proportions of patients with post-Baseline PCS values were generally low. Evaluation of liver enzymes did not show any clinically relevant findings. No patients met the criteria for Hy's law.
- One patient in the EPTI100-EPTI100 group had *wish to be dead* as assessed using the C-SSRS.

Immunogenicity Results

- During the Placebo-controlled Period, 7 patients were ADA-positive at any time point; of those, 1 patient had pre-treatment ADAs which was not boosted following treatment. At Week 12, 7 patients (8.5%) in the EPTI100 group were ADA-positive (median titre of 134 [ranging from 71 to 1230]); of those, 3 patients (43%) were NAb positive.
- During the Open-label Period, 10 patients (14%) and 14 patients (21%) in the PBO-EPTI100 and EPTI100-EPTI100 group, respectively, were ADA-positive at any time point; of those, 7 patients (70%) and 4 patients (29%) in the PBO-EPTI100 and EPTI100-EPTI100 group, respectively, were NAb-positive.
- Overall, the onset of treatment-induced ADAs was observed at Week 12 after the first administration of the IMP, and the highest proportions of ADA-positive patients were observed at Week 20 (Safety-follow Up Visit) for the PBO-EPTI100 (14%) group and at Week 24 for the EPT100-EPTI100 group (20%); the highest median ADA titre was observed for the PBO-EPTI100 group at the Safety Follow-up Visit (523; ranging from 99 to 2200).
- The assessment of the TEAEs in patients who were ADA-positive did not indicate safety signals related to ADA development.

Conclusions

- In the primary analysis of the primary endpoint, eptinezumab 100 mg did not demonstrate a statistically significant difference to placebo based on the mean change from Baseline in MMDs. The mean change from Baseline in MMDs (Weeks 1-12) was numerically in favour of eptinezumab 100 mg.
- In general, the results of the key secondary, secondary, and exploratory efficacy analyses were consistent with those of the primary efficacy analysis. For the majority of the key secondary, secondary, and exploratory endpoints, the improvements were consistently numerically in favour of eptinezumab 100 mg.
- Eptinezumab was well tolerated when administered to patients with a dual diagnosis of migraine and MOH. The safety and tolerability profile of eptinezumab was comparable to that observed previously with eptinezumab in patients with migraine.
- No safety signals related to ADA development were identified.

Report Date

10 July 2023

This study was conducted in compliance with *Good Clinical Practice*.