Synopsis – Study 18898A

Study Title Interventional, randomized, double-blind, parallel-group, placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments
Investigators 96 principal investigators at 96 sites in 17 countries *Signatory investigator* – [redacted]
Study Sites 96 sites – 4 in Belgium, 6 in Bulgaria, 14 in Czech Republic, 2 in Denmark, 4 in Finland, 6 in France, 9 in Georgia, 6 in Germany, 2 in Hungary, 3 in Italy, 18 in Poland, 1 in Russian Federation, 4 in Slovakia, 8 in Spain, 1 in Sweden, 5 in United Kingdom, and 3 in United States
Publications • Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen CL, Josiassen MK, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2022 Jul;21(7):597-607. • Ashina M, Lanteri-Minet M, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, et al. Efficacy and safety of eptinezumab for migraine prevention in patients with prior preventive treatment failures: subgroup analysis of the randomized, placebo-controlled DELIVER study. Cephalalgia. 2023 May;43(5):3331024231170807. • Barbanti P, Goadsby PJ, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, et al. Effects of eptinezumab on self-reported work productivity in adults with migraine and prior preventive treatment failure in the randomized, double-blind, placebo-controlled DELIVER study. J Headache Pain. 2022 Dec2;23(1):153. • Fawsitt CG, Thom H, Regnier SA, Lee XY, Kymes S, Vase L. Comparison of indirect treatment methods in migraine prevention to address differences in mode of administration. J Comp Eff Res. 2023 May 24:e230021. • Goadsby PJ, Barbanti P, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, et al. Eptinezumab improved patient-reported outcomes and quality of life in patients with migraine and prior preventive treatment failures. Eur J Neurol. 2023 Apr;30(4):1089-1098. • Jönsson L, Regnier SA, Kymes S, Awad SF, Talon B, Lee XY, et al. Estimating treatment effects on health utility scores for patients living with migraine: a post hoc analysis of the DELIVER trial. Expert Rev Pharmacoecon Outcomes Res. 2023 Jun 2:1-7.
Study Period *First patient first visit* – 1 June 2020 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 15 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 in patients with unsuccessful prior preventive treatments	• Primary endpoint: – change from Baseline in *monthly migraine days* (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 1-12) – change from Baseline in MMDs (Weeks 13-24) • Secondary endpoints: – response: ≥50% reduction from Baseline in MMDs (Weeks 13-24) – response: ≥75% reduction from Baseline in MMDs (Weeks 13-24) – response: 100% reduction from Baseline in MMDs (average of 4-weekly results, across Weeks 1-12) – response: ≥50% reduction from Baseline in *monthly headache days* (MHDs) (Weeks 1-12) – response: ≥75% reduction from Baseline in MHDs (Weeks 1-12) – response: 100% reduction from Baseline in MHDs (average of 4-weekly results, across Weeks 1-12) – change from Baseline in MHDs (Weeks 1-12) – change from Baseline in the percentage of migraines/headaches with severe pain intensity (Weeks 1-12) – change from Baseline in monthly days with use of acute migraine medication (Weeks 1-12) – change from Baseline in monthly days with use of acute migraine medication (Weeks 13-24) – change from Baseline in MMDs with use of acute medication (Weeks 1-12) – change from Baseline in MMDs with use of acute medication (Weeks 13-24) – Patient Global Impression of Change (PGIC) score at Week 12 – PGIC score at Week 24 – change from Baseline in MMDs in patients with medication overuse headache (MOH) (Weeks 1-12) – migraine on the day after first dosing – most bothersome symptom (MBS) score at Week 12, as measured relative to Baseline

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Primary Objective (continued)	• Exploratory endpoints: – change from Baseline in monthly *headache episodes* for each 12-week period – change from Baseline in monthly *migraine attacks* for each 12-week period – response: 100% reduction from Baseline in MMDs (average of 4-weekly results, across Weeks 13-24) – response: ≥50% reduction from Baseline in MHDs (Weeks 13-24) – response: ≥75% reduction from Baseline in MHDs (Weeks 13-24) – response: 100% reduction from Baseline in MHDs (average of 4-weekly results, across Weeks 13-24) – change from Baseline in the percentage of migraine/headaches with severe pain intensity (Weeks 13-24) – change from Baseline in MMDs in patients with MOH (Weeks 13-24) – MBS score at Week 24, as measured relative to Baseline
Secondary Objectives • to evaluate the health-related quality of life and work productivity impact of eptinezumab	• Key secondary endpoint: – change from Baseline to Week 12 in the Headache Impact Test (HIT-6) score • Secondary endpoints: – change from Baseline to Week 24 in the HIT-6 score – change from Baseline to Week 12 in the Migraine-Specific Quality of Life (MSQ) 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 Resources Utilization (HCRU) at Week 12 – change from Baseline to Week 24 in the MSQ subscores – change from Baseline to Week 24 in the EQ-5D-5L VAS score – HCRU at Week 24 – change from Baseline to Week 12 in the Work Productivity and Activity Impairment (WPAI) questionnaire subscores (*Absenteeism*, *Presenteeism*, *Work Productivity Loss*, *Activity Impairment*) – change from Baseline to Week 24 in the WPAI subscores – response: ≥5-point reduction from Baseline to Week 12 in HIT-6 score – response: ≥5-point reduction from Baseline to Week 24 in HIT-6 score
• to evaluate the effect of long-term treatment with eptinezumab	• Secondary endpoints: – change from Baseline in MMDs (Weeks 25 to 36, 37 to 48, 49 to 60, 61 to 72) – response: ≥50% reduction from Baseline in MMDs (Weeks 25 to 36, 37 to 48, 49 to 60, 61 to 72) – response: ≥75% reduction from Baseline in MMDs (Weeks 25 to 36, 37 to 48, 49 to 60, 61 to 72) – change from Baseline in the HIT-6 score (at Weeks 36, 48, 60, and 72)

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
Secondary Objectives (continued)	• Exploratory endpoints: – response: 100% reduction from Baseline in MMDs (average of 4-weekly results, across Weeks 25-36, 37-48, 49-60, 61-72) – response: ≥50% reduction from Baseline in MHDs (Weeks 25-36, 37-48, 49-60, 61-72) – response: ≥75% reduction from Baseline in MHDs (Weeks 25-36, 37-48, 49-60, 61-72) – response: 100% reduction from Baseline in MHDs (average of 4-weekly results, across Weeks 25-36, 37-48, 49-60, 61-72) – change from Baseline in MHDs (Weeks 13-24, 25-36, 37-48, 49-60, 61-72) – change from Baseline in the percentage of migraine/headaches with severe pain intensity (Weeks 25-36, 37-48, 49-60, 61-72) – change from Baseline in monthly days with use of acute migraine medication (Weeks 25-36, 37-48, 49-60, 61-72) – change from Baseline in MMDs with use of acute migraine medication (Weeks 25-36, 37-48, 49-60, 61-72) – PGIC score (at Weeks 36, 48, 60, and 72) – change from Baseline in MMDs in patients with MOH (Weeks 25-36, 37-48, 49-60, 61-72) – MBS score as measured relative to Baseline (at Weeks 36, 48, 60, and 72) – change from Baseline in monthly *migraine attacks* for each 12-week period (Weeks 25-36, 37-48, 49-60, 61-72) – change from Baseline in monthly *headache episodes* for each 12-week period (Weeks 25-36, 37-48, 49-60, 61-72) – change from Baseline in the MSQ subscores (at Weeks 36, 48, 60, and 72) – change from Baseline in the EQ-5D-5L VAS score (at Weeks 36, 48, 60, and 72) – HCRU (at Weeks 36, 48, 60, and 72) – change from Baseline in the WPAI subscores (at Weeks 36, 48, 60, and 72) – response: ≥5-point reduction from Baseline to Week 36, 48, 60, and 72 in HIT-6 score
Safety Objectives • to evaluate the safety and tolerability of eptinezumab • to evaluate the long-term 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 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 – 24-week double-blind treatment period with placebo or eptinezumab
  - Extension Period – 48-week dose-blinded period with eptinezumab after completion of the Placebo-controlled Period
- Placebo-controlled Period: the patients were randomized 1:1:1 to 24 weeks of double-blind treatment with placebo, eptinezumab 100 mg, or eptinezumab 300 mg; the corresponding treatment groups are referred to as PBO, EPTI100, and EPTI300. Randomization was stratified by country and by number of MHDs at baseline (≤14 MHDs/>14 MHDs). The patients received investigational medicinal product (IMP) by intravenous (IV) infusion over 30 minutes (up to 45 minutes), starting from the Baseline Visit; hereafter, the patients were dosed every 12 weeks (that is, a total of two doses).
- Extension Period: After 24 weeks, the patients entered the dose-blinded Extension Period. Patients assigned to placebo in the Placebo-controlled Period were randomized 1:1 to treatment with either eptinezumab 100 mg or eptinezumab 300 mg; the corresponding treatment groups are referred to as PBO-EPTI100 and PBO-EPTI300. Patients assigned to eptinezumab 100 mg or 300 mg in the Placebo-controlled Period continued their treatment; the corresponding treatment groups are referred to as EPTI100-EPTI100 and EPTI300-EPTI300. In the Extension Period, the focus is on the treatment (eptinezumab 100 mg or eptinezumab 300 mg) received in the Extension Period, not the treatment received in the Placebo-controlled Period, as this period is of considerably shorter duration; the corresponding treatment groups are referred to as EPTI100 and EPTI300. The patients were dosed every 12 weeks, starting at Week 24. Patients who completed the Extension Period received six doses in total (that is, two doses in the Placebo-controlled Period and four doses in the Extension Period).
- The eDiary was completed from the time of screening until the Completion/Withdrawal Visit. Other efficacy data were collected at Baseline and all subsequent visits. Safety assessments were performed throughout the study.

Number of Patients Planned

840 patients were planned for randomization, with 280 patients in each treatment group.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of migraine according to Headache Classification Committee of the International Headache Society, the International Classification of Headache Disorders, 3rd edition 2018 criteria, who:

- fulfilled the criteria for chronic migraine (CM) or episodic migraine (EM), with ≥4 MMDs, based on prospectively collected information in the eDiary during the Screening Period
- had a history of CM or EM for at least 12 months prior to the Screening Visit
- had documented evidence of failure to 2 to 4 different preventive migraine medications in the past 10 years
- were ≥18 and ≤75 years of age

Investigational Medicinal Products (IMPs), Doses and Mode of Administration, Batch Numbers

Eptinezumab – 100 mg or 300 mg; concentrate for solution for infusion, 100 mg/mL added to 100 mL of 0.9% saline solution, IV; batch Nos. APSG01, APTC02

Control Product, Dose and Mode of Administration

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

Duration of Treatment

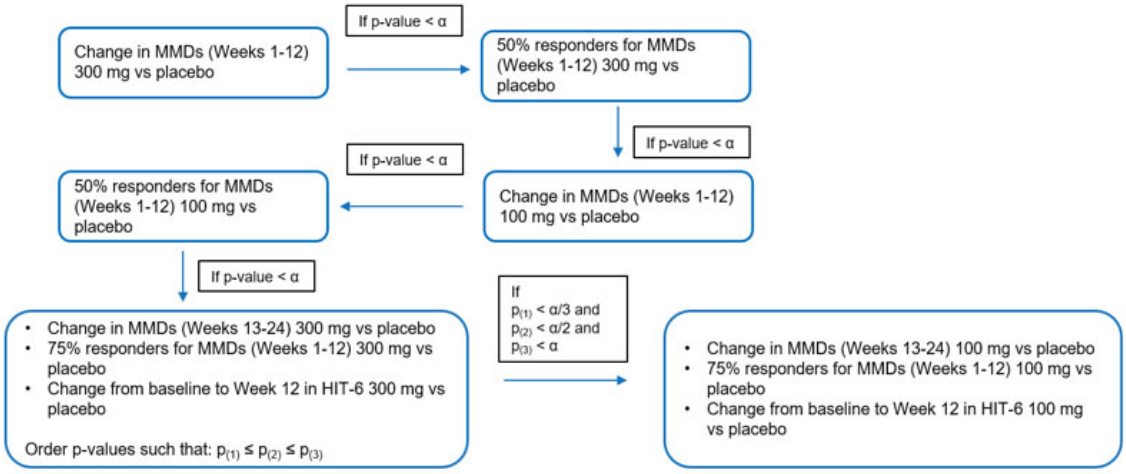
Placebo-controlled Period: 24 weeks; Extension Period: 48 weeks

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 at least one infusion of the 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-long-term set* (APTS_LT) – all patients in the APRS who received at least one infusion of the IMP and had a visit in the Extension Period
  - *full-analysis-long-term set* (FAS_LT) – all patients in the APTS_LT who had a valid Baseline assessment and a valid assessment of MMDs in the Extension Period
- Unless otherwise specified, the efficacy and pharmacoeconomic analyses and data presentations are based on the FAS for the Placebo-controlled Period and FAS_LT for the Extension Period; the safety analyses and data presentations are based on the APTS for the Placebo-controlled Period and APTS_LT for the Extension Period.
- Changes from Baseline in MMDs for the 6 first 4-week intervals were analysed using a restricted maximum likelihood-based mixed model for repeated measures (MMRM). The model included the fixed effects of month (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24), country, stratification (MHDs at Baseline: ≤14 MHDs/>14 MHDs), and treatment as factors; baseline MMDs as a continuous covariate; treatment-by-month interaction; baseline score-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 estimand for the primary endpoint was the effect of eptinezumab on the number of MMDs that was seen in the hypothetical case where no acute medication was available if patients who withdrew due to lack of efficacy remained on their current trajectory, if patients who withdrew due to adverse events at an early stage were considered as obtaining only limited improvement in their Baseline disease level, and if the effect was considered regardless of use of preventive medication and infusion interruptions or terminations.
  - The intercurrent events addressed were:
    - use of acute medication to treat a headache
    - use of preventive migraine medication
    - withdrawal due to lack of efficacy
    - withdrawal due to an adverse event
    - withdrawal due to other reasons
    - interruption/termination of infusions
  - The attributes for the estimand included:
    - *treatment condition* – comparing eptinezumab 100 mg and 300 mg to placebo
    - *population* – as defined in the inclusion and exclusion criteria
    - endpoint – the change from Baseline in MMDs across Weeks 1-12
    - *population-level summary* – the least squares mean difference between eptinezumab and placebo for the endpoint
- The mean difference between each dose of eptinezumab and placebo was estimated based on the least squares means for the treatment-by-month interaction in the MMRM. The primary comparisons were the contrasts between each dose of eptinezumab and placebo averaged across Weeks 1-12.
- Sensitivity and supplementary analyses for the primary endpoint were performed.
- The key secondary endpoints related to 50% and 75% response were analysed using logistic regression with baseline MMDs as a continuous covariate and treatment and stratification (MHDs at Baseline: ≤14 MHDs/>14 MHDs) as factors. The logistic regression model was fitted using the maximum likelihood method and the logit link function.

Statistical Methodology (continued)

- The key secondary endpoint, change from Baseline in MMDs (Weeks 13-24), was analysed using the same MMRM as for the primary endpoint. The comparisons were the contrasts between each dose of eptinezumab and placebo averaged across Weeks 13-24.
- The key secondary endpoint, change from Baseline to Week 12 in HIT-6 score, was analysed using an MMRM similar to the one used for the primary endpoint. All the visits from the Placebo-controlled Period were included in the analysis. The comparisons were the contrasts between each dose of eptinezumab and placebo at Week 12.
- Sensitivity analyses for each key secondary endpoint were performed.
- The testing strategy was a sequence of tests, either testing one endpoint at a time or using the Bonferroni-Holm method to test a group of endpoints. 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 schematic overview of the steps is presented below:



- For the last two steps, the Bonferroni-Holm method was used to test the group of endpoints. The consecutive order of the smallest ($p_{(1)}$), the second smallest ($p_{(2)}$), and the largest p-value ($p_{(3)}$) had to be $<\alpha/3$, $<\alpha/2$, and $<\alpha$, where $\alpha = 0.05$, respectively, in favour of the dose tested to consider the effect on all three key secondary endpoints to be statistically significant. Statistical significance could be established for the individual endpoints even if the testing did not continue; for example, for the endpoint related to $p_{(1)}$ (if $p_{(1)} <\alpha/3$, even if $p_{(2)} \geq\alpha/2$), or the endpoints related to $p_{(1)}$ and $p_{(2)}$ (if $p_{(1)} <\alpha/3$ and $p_{(2)} <\alpha/2$, even if $p_{(3)} \geq\alpha$).
- The power was determined by simulations of the endpoints in the testing strategy. Randomization of 280 patients per treatment group provided approximately 94% power for the comparison of eptinezumab 100 mg to placebo and 99% power for the comparison of eptinezumab 300 mg to placebo. This sample size also provided at least 68% power for the individual key secondary endpoints for showing an effect, with a combined power of 58% for seeing an effect on all primary and key secondary endpoints and both doses in the testing strategy.
- The eDiary-derived secondary and exploratory endpoints were analysed using an MMRM similar to the one specified for the primary endpoint. The exploratory endpoints related to response were analysed using a logistic regression model similar to the one specified for the key secondary endpoints (50% and 75% response) or an extended Cochran-Mantel-Haenszel test similar to the one specified for the secondary endpoints (migraine on the day after first dosing and 100% response).
- The overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal in the Placebo-controlled Period and in the Extension Period were summarized by primary system organ class (SOC) and preferred term.
- Adverse events, clinical safety laboratory test values, vital signs, body measurements (height, weight, body mass index), ECG parameters, and C-SSRS scores were summarized using descriptive statistics.

Patient Disposition and Analysis Sets

• Patient disposition in the Placebo-controlled Period is summarized below:

	PBO		EPTI 100mg		EPTI 300mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomized	299		299		294		892	
Patients treated (APTS)	298		299		294		891	
Patients completed	293	(98.3)	288	(96.3)	284	(96.6)	865	(97.1)
Patients withdrawn	5	(1.7)	11	(3.7)	10	(3.4)	26	(2.9)
Primary reason for withdrawal:								
Adverse event	1	(0.3)	1	(0.3)	6	(2.0)	8	(0.9)
Lack of efficacy	1	(0.3)	3	(1.0)	0		4	(0.4)
Protocol violation	0		1	(0.3)	1	(0.3)	2	(0.2)
Withdrawal of consent	1	(0.3)	5	(1.7)	2	(0.7)	8	(0.9)
Lost to follow-up	0		1	(0.3)	0		1	(0.1)
Other	2	(0.7)	0		1	(0.3)	3	(0.3)
Analysis sets:								
APRS	299		299		294		892	
APTS	298		299		294		891	
FAS	298		299		293		890	

• Patient disposition in the Extension Period is summarized below:

	EPTI 100mg		EPTI 300mg		Total	
	n	(%)	n	(%)	n	(%)
Patients treated (APTS_LT)	433		432		865	
Patients completed	392	(90.5)	390	(90.3)	782	(90.4)
Patients withdrawn	41	(9.5)	42	(9.7)	83	(9.6)
Primary reason for withdrawal:						
Adverse event	3	(0.7)	9	(2.1)	12	(1.4)
Lack of efficacy	14	(3.2)	13	(3.0)	27	(3.1)
Non-compliance with IMP	0		2	(0.5)	2	(0.2)
Protocol violation	0		2	(0.5)	2	(0.2)
Withdrawal of consent	23	(5.3)	18	(4.2)	41	(4.7)
Other	5	(1.2)	2	(0.5)	7	(0.8)
Analysis sets:						
APTS_LT	433		432		865	
FAS_LT	430		428		858	

Demographics and Baseline Characteristics of the Study Population

- Demographics were comparable across treatment groups: the mean age of the patients was 44 years, and the majority of the patients were women (90%); in the age subgroup >35 years old (78%); White (96%); and enrolled in sites in Europe (99%), primarily in Poland (29%), the Czech Republic (24%), and Georgia (20%).
- Overall, the demographics at Baseline for the patients who continued in the Extension 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 (CM or EM) was 18 years, and the mean age at first diagnosis of migraine was 26 years.
- Based on the eDiary data, collected in the Screening Period, 54% of the patients were classified as having EM and 46% were classified as having CM.
- Twelve percent of the patients had a dual diagnosis of migraine and MOH diagnosed at the Screening Visit. Thirty percent of the patients had a diagnosis of migraine with aura and a small proportion (5.2%) of the patients had aura symptoms without headache.
- The pattern and nature of prior treatment failures were similar across treatment groups. The majority (62%) of the patients had 2 previous treatment failures; 31% of the patients had 3 previous treatment failures and 6.7% of the patients had 4 previous treatment failures. The most common types of treatment failures were lack of efficacy (100%) and safety/tolerability issues (56%). The most common types of treatment failure medications were topiramate (71%) and amitriptyline (57%).
- At Baseline, the patients had a mean of 14 MMDs (≥8 MMDs is considered *severe*).
- The mean HIT-6 score was 66 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 36 to 51 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 indicated 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.
- At Baseline, approximately 8% of the patients had concurrent diagnosis of hypertension.

Efficacy and Pharmacoeconomic Results

- Statistically significant treatment effects (p <0.0001) favouring eptinezumab 100 and 300mg were seen for all the efficacy analyses included in the testing strategy.
- The testing strategy results are summarized below:

Endpoint	N	Mean[a]	Difference to Placebo (CI)	Responders (%)	Odds Ratio (CI)	p-value
Change from Baseline in MMDs (Weeks 1-12)						
PBO	298	-2.1				
EPTI 300mg	293	-5.3	-3.2 (-3.9; -2.5)			<0.0001
Since p-value <0.05, the testing continued as follows:						
≥50% reduction from Baseline in MMDs (Weeks 1-12)						
PBO	298	13.1				
EPTI 300mg	293	49.5		49.5	6.58 (4.41; 10.01)	<0.0001
Since p-value <0.05, the testing continued as follows:						
Change from Baseline in MMDs (Weeks 1-12)						
PBO	298	-2.1				
EPTI 100mg	299	-4.8	-2.7 (-3.4; -2.0)			<0.0001
Since p-value <0.05, the testing continued as follows:						
≥50% reduction from Baseline in MMDs (Weeks 1-12)						
PBO	298	13.1				
EPTI 100mg	299	42.1		42.1	4.91 (3.29; 7.47)	<0.0001
Since p-value <0.05, the testing continued as follows:						
Change from Baseline in MMDs (Weeks 13-24)						
PBO	295	-2.4				
EPTI 300mg	286	-6.1	-3.7 (-4.5; -3.0)			<0.0001
≥75% reduction from Baseline in MMDs (Weeks 1-12)						
PBO	298	2.0				
EPTI 300mg	293	18.8		18.8	11.43 (5.22; 30.15)	<0.0001
Change from Baseline to Week 12 in the HIT-6 score						
PBO	288	-3.1				
EPTI 300mg	283	-8.5	-5.4 (-6.7; -4.2)			<0.0001
Since $p_{(1)}$ <0.05/3 and $p_{(2)}$ <0.05/2 and $p_{(3)}$ <0.05, the testing continued as follows:						
Change from Baseline in MMDs (Weeks 13-24)						
PBO	295	-2.4				
EPTI 100mg	287	-5.4	-3.0 (-3.8; -2.2)			<0.0001
≥75% reduction from Baseline in MMDs (Weeks 1-12)						
PBO	298	2.0				
EPTI 100mg	299	15.7		15.7	9.19 (4.16; 24.35)	<0.0001
Change from Baseline to Week 12 in the HIT-6 score						
PBO	288	-3.1				
EPTI 100mg	277	-6.9	-3.8 (-5.0; -2.5)			<0.0001

CI = confidence interval; $p_{(1)}$ = the smallest p-value; $p_{(2)}$ = the second smallest p-value; $p_{(3)}$ = the largest p-value

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

Efficacy and Pharmacoeconomic Results (continued)

- The mean change from Baseline to Week 12 in MMDs was -2.1, -4.8, and -5.3 days for placebo, eptinezumab 100mg, and eptinezumab 300mg, respectively. In the primary analysis of the primary endpoint (FAS, MMRM) (the mean change from Baseline in MMDs [Weeks 1-12]), both doses of eptinezumab demonstrated a clinically meaningful difference to placebo (-2.7 and -3.2 days, respectively; $p < 0.0001$). The results of the sensitivity analyses and the supplementary analyses of the primary endpoint were consistent with the results of the primary analyses. The reduction in MMDs seen for patients treated with eptinezumab in the Placebo-controlled Period was maintained in the Extension Period. Throughout the Extension Period, the mean changes from Baseline in MMDs ranged between -5.8 and -6.6 days for the patients treated with eptinezumab 100mg and between -5.9 and -6.5 days for the patients treated with eptinezumab 300mg. A similar level of reduction in MMDs was seen in the patients who changed treatment from placebo in the Placebo-controlled Period to eptinezumab 100mg or 300mg in the Extension Period.
- In all the analyses of the key secondary endpoints, the treatment effects were in favour of both doses of eptinezumab ($p < 0.0001$). There were clinically relevant differences in the proportions of responders during Weeks 1-12. The proportion of patients who had a ≥50% reduction from Baseline in MMDs was 13%, 42%, and 50% for the PBO, EPTI100, and EPTI300 mg groups, respectively, and the proportion of patients who had a ≥75% reduction from Baseline in MMDs was 2%, 16%, and 19% in the placebo, EPTI100, and EPTI300 groups, respectively. Furthermore, the difference to placebo in the change from Baseline in MMDs during Weeks 1-12 was sustained during Weeks 13-24 for both doses of eptinezumab. Finally, the patients' self-reported ability to function normally in daily life as assessed using the change from Baseline to Week 12 in the HIT-6 score was clinically relevantly greater for both doses of eptinezumab than for placebo; the mean difference to placebo was -3.8 and -5.4 points for the EPTI100 and EPTI300 groups, respectively.
- The results of the analyses of the secondary and exploratory endpoints based on the eDiary-derived variables including response were consistent with the results of the primary analysis and showed greater improvement for both doses of eptinezumab than for placebo during Weeks 1-12 and Weeks 13-24 ($p < 0.0001$ for the vast majority of endpoints). On the first day after dosing (Day 1), the proportion of patients with migraine was lower ($p < 0.0001$) for both doses of eptinezumab than for placebo. For the patients treated with eptinezumab in the Placebo-controlled Period, the improvements seen in the Placebo-controlled Period were maintained during the Extension Period for all endpoints related to eDiary-derived variables. A similar level of improvement was seen in the patients who changed treatment from placebo in the Placebo-controlled Period to eptinezumab 100mg or 300mg in the Extension Period.
- The results of the analyses of the secondary and exploratory endpoints based on the PGIC, MBS, MSQ, and HIT-6 were consistent with the results of the primary analysis and showed greater improvement for both doses of eptinezumab than for placebo ($p < 0.0001$) at Weeks 12 and 24. The results indicated greater improvement in the EPTI groups than in the PBO group in the patients' perceived impact of migraine (based on the PGIC), their identified MBS (based on the MBS), and their quality of life (based on the MSQ). The change from Baseline to Week 24 in the HIT-6 score indicated larger reductions in the impact of headache during attacks for both doses of eptinezumab than for placebo. At Weeks 12 and 24, the proportions of patients with a ≥5-point reduction in the HIT-6 score were higher for both doses of eptinezumab than for placebo.
- 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 and showed greater improvement for both doses of eptinezumab than for placebo ($p < 0.05$) at Weeks 12 and 24. The results indicated greater improvement in work productivity and activity impairment (based on the WPAI) for both doses of eptinezumab than for placebo. The mean change in the EQ-5D-5L VAS score showed numerical improvement in well-being in the EPTI groups and numerical deterioration in the PBO group. For the patients treated with eptinezumab in the Placebo-controlled Period, the improvement seen in the Placebo-controlled Period were maintained during the Extension Period for the endpoints related to PGIC and MBS and for the pharmacoeconomic endpoints (HIT-6, MSQ, EQ-5D-5L VAS, and WPAI). A similar level of improvement was seen in the patients who changed treatment from placebo in the Placebo-controlled Period to eptinezumab 100mg or 300mg in the Extension Period.
- The information related to HCRU indicated that, overall, the patients' use of health care resources decreased in all the treatment groups from Baseline to Weeks 12 and 24; in addition, health care resource use was numerically lower in the EPTI groups than in the PBO group during the Placebo-controlled Period. The HCRU also decreased in the Extension Period in both EPTI groups.

Safety Results

Placebo-controlled Period

- The adverse event incidence during the Placebo-controlled Period is summarized below:

	PBO			EPTI 100mg			EPTI 300mg		
	n	(%)	E	n	(%)	E	n	(%)	E
Patients treated	298			299			294		
Patients who died	0			0			0		
SAEs	3	(1.0)	5	6	(2.0)	7	7	(2.4)	8
TEAEs	119	(39.9)	234	129	(43.1)	230	122	(41.5)	270
TEAEs leading to IMP infusion interruption/termination	0			1	(0.3)	1	3	(1.0)	3
TEAEs leading to withdrawal	1	(0.3)	1	1	(0.3)	1	6	(2.0)	6

n = number of patients; % = incidence of adverse events; E = number of adverse events

- The overall incidence of TEAEs was approximately 40% and evenly distributed across treatment groups. The overall incidences of SAEs and TEAEs leading to withdrawal were low and highest in the EPTI100 and EPTI300 groups.
- The SOC with the highest incidence of TEAEs (14% to 18% across treatment groups) was *infections and infestations*. Within all the other SOCs, the incidences of TEAEs did not exceed 8.0% in any treatment group and were generally balanced across treatment groups.
- TEAEs with an incidence ≥1.5% in any treatment group during the Placebo-controlled Period are summarized below:

Preferred Term (MedDRA Version 25.0)	PBO		EPTI 100mg		EPTI 300mg	
	n	(%)	n	(%)	n	(%)
Patients treated	298		299		294	
Covid-19	16	(5.4)	20	(6.7)	17	(5.8)
Nasopharyngitis	3	(1.0)	5	(1.7)	9	(3.1)
Fatigue	4	(1.3)	2	(0.7)	6	(2.0)
Diarrhoea	5	(1.7)	0		5	(1.7)
Dizziness	5	(1.7)	2	(0.7)	5	(1.7)
Nausea	4	(1.3)	4	(1.3)	5	(1.7)
Urinary Tract Infection	5	(1.7)	1	(0.3)	5	(1.7)
Abdominal Pain Upper	2	(0.7)	5	(1.7)	4	(1.4)
Arthralgia	0		6	(2.0)	4	(1.4)
Back Pain	4	(1.3)	6	(2.0)	3	(1.0)

- The most common TEAE was *coronavirus disease 2019* (*COVID-19*), with an incidence of approximately 6% in each treatment group. Except for *COVID-19* and *nasopharyngitis* (the incidence of *nasopharyngitis* ranged from 1% in the PBO group to 3.1% in the EPTI300 group), none of the TEAEs had an incidence >2% in any treatment group. For the vast majority of the patients with TEAEs, the TEAEs were *mild* or *moderate*; the incidence of *severe* TEAEs ranged from 0.7% (PBO group) to 2.4% (EPTI300 group). No *severe* TEAE occurred in more than 1 patient in any treatment group.
- The overall incidence of treatment-emergent adverse events of special interest (AESIs) was low, and most of the events were *mild* or *moderate*. The only treatment-emergent AESIs that were *serious* and led to withdrawal from the study were 2 SAEs of *anaphylactic reaction* (both in the EPTI300 group) considered *related* to IMP. Further, there were 2 SAEs, 1 of *suicidal ideation* (in the PBO group) and 1 of *seizure* (in the EPTI300 group), both considered *not related* to IMP, that did not lead to withdrawal from the study, and 1 non-serious event of *hypersensitivity* (in the EPTI100 group) that led to withdrawal from the study. The incidence of *cardio-/cerebrovascular events* was low and comparable across treatment groups.
- None of the patients died. A total of 16 patients had treatment-emergent SAEs: 3 in the PBO group, 6 in the EPTI100 group, and 7 in the EPTI300 group. Only *anaphylactic reaction* (2 patients in the EPTI300 group) and *COVID-19* (1 patient in the EPTI100 group and 2 in the EPTI300 group) occurred in >1 patient in any treatment group.

Safety Results (continued)

Placebo-controlled Period

- One patient (in the EPTI300 group) became pregnant. The outcome of the pregnancy is unknown as the patient did not consent to provide this information.
- A total of 4 patients had TEAEs that led to interruption or termination of the IMP infusion but not withdrawal from the study: in the EPTI300 group, 1 patient had *moderate infusion site extravasation* and 1 patient had *mild nausea*. Two patients, 1 in each of the EPTI groups, had *mild circulatory collapse*. All the affected patients recovered, and they all received their second dose of IMP without adverse events considered *related* to the infusion.
- A total of 8 patients, 6 of whom were in the EPTI300 group, had TEAEs that led to withdrawal. Only *anaphylactic reaction* occurred in >1 patient in any treatment group.
- 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 patients with post-Baseline PCS values across the variables were generally low and with 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.
- Only 1 patient (in the PBO group) had any suicidal ideation or behaviour (*non-specific active suicidal thoughts*) as assessed using the C-SSRS; this patient also had the SAE of *suicidal ideation* and did not withdraw from the study.

Extension Period

- The adverse event incidence during the Extension Period is summarized below:

	PBO-EPTI100			PBO-EPTI300			EPTI100-EPTI100			EPTI300-EPTI300		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Patients treated	145			148			288			284		
Patients who died	0			0			0			0		
SAEs	2	(1.4)	2	7	(4.7)	9	9	(3.1)	12	9	(3.2)	11
TEAEs	72	(49.7)	151	81	(54.7)	208	159	(55.2)	388	148	(52.1)	394
TEAEs leading to IMP infusion interruption/termination	0			0			1	(0.3)	1	1	(0.4)	1
TEAEs leading to withdrawal	0			3	(2.0)	3	3	(1.0)	3	6	(2.1)	6

n = number of patients; % = incidence of adverse events; E = number of adverse events

- The overall incidence of TEAEs was approximately 53% and evenly distributed across treatment groups. The overall incidences of SAEs and TEAEs leading to withdrawal were low and highest in the PBO-EPTI300 (SAEs and TEAEs leading to withdrawal) and EPTI300-EPTI300 (TEAEs leading to withdrawal) groups.
- The SOC with the highest incidence of TEAEs (29% to 37% across treatment groups) was *infections and infestations*. Within all the other SOCs, the incidences of TEAEs did not exceed 10% in any treatment group and were generally balanced across treatment groups.

Safety Results (continued)

Extension Period

• TEAEs with an incidence ≥1.5% in any treatment group during the Extension Period are summarized below:

Preferred Term	PBO-EPTI100		PBO-EPTI300		EPTI100-EPTI100		EPTI300-EPTI300	
(MedDRA Version 25.0)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	145		148		288		284	
Covid-19	25	(17.2)	31	(20.9)	63	(21.9)	63	(22.2)
Nasopharyngitis	7	(4.8)	13	(8.8)	19	(6.6)	27	(9.5)
Upper Respiratory Tract Infection	4	(2.8)	6	(4.1)	13	(4.5)	8	(2.8)
Arthralgia	1	(0.7)	2	(1.4)	6	(2.1)	6	(2.1)
Pruritus	1	(0.7)	0		2	(0.7)	6	(2.1)
Dyspepsia	0		1	(0.7)	1	(0.3)	5	(1.8)
Gastroenteritis	1	(0.7)	1	(0.7)	3	(1.0)	5	(1.8)
Post Vaccinatinon Syndrome	0		1	(0.7)	0		5	(1.8)
Sinusitis	2	(1.4)	2	(1.4)	4	(1.4)	5	(1.8)
Urinary Tract Infection	3	(2.1)	4	(2.7)	3	(1.0)	5	(1.8)
Pharyngitis	0		3	(2.0)	3	(1.0)	4	(1.4)
Abdominal Pain Upper	1	(0.7)	3	(2.0)	4	(1.4)	3	(1.1)
Bronchitis	1	(0.7)	3	(2.0)	4	(1.4)	3	(1.1)
Cystitis	0		5	(3.4)	1	(0.3)	3	(1.1)
Migraine	0		1	(0.7)	7	(2.4)	3	(1.1)
Nausea	1	(0.7)	5	(3.4)	2	(0.7)	3	(1.1)
Back Pain	1	(0.7)	2	(1.4)	8	(2.8)	2	(0.7)
Fatigue	0		1	(0.7)	5	(1.7)	2	(0.7)
Hypertension	3	(2.1)	0		3	(1.0)	2	(0.7)
Menopause	1	(0.7)	3	(2.0)	1	(0.3)	0	

• The most common TEAE was *COVID-19*, with an incidence of approximately 21%. Except for *COVID-19* and *nasopharyngitis* (the incidence of *nasopharyngitis* ranged from 4.8% in the PBO-EPTI100 group to 9.5% in the EPTI300-EPTI300 group), none of the TEAEs had an incidence >5% in any treatment group. For the vast majority of the patients with TEAEs, the TEAEs were *mild* or *moderate*; the incidence of *severe* TEAEs ranged from 0.7% (PBO-EPTI100 group) to 5.4% (PBO-EPTI300 group). Except for *migraine*, no *severe* TEAE occurred in more than 1 patient in any treatment group.

• The overall incidence of treatment-emergent AESIs was low, and most of the events were *mild* or *moderate*. The only treatment-emergent AESIs that were *serious* and led to withdrawal from the study were 1 SAE of *anaphylactic reaction* and 1 SAE of *bronchospasm* (both in the PBO-EPTI300 group), both considered *related* to IMP. Further, there were 2 SAEs, 1 of *acute myocardial infarction* (in the EPTI300-EPTI300 group) and 1 of *intracranial aneurysm* (in the EPTI100-EPTI100 group) that were considered *not related* to IMP and did not lead to withdrawal from the study. The incidence of *cardio-/cerebrovascular events* was low and comparable with that in the Placebo-controlled Period.

• None of the patients died. A total of 27 patients had treatment-emergent SAEs: 2 in the PBO-EPTI100 group, 7 in the PBO-EPTI300 group, and 9 in each of the EPTI100-EPTI100 and EPTI300-EPTI300 groups. None of the SAEs occurred in >1 patient in any treatment group.

• Two patients in the EPTI300-EPTI300 group became pregnant. One patient had a healthy baby. One patient had a spontaneous abortion. The spontaneous abortion was considered *not related* to IMP.

• A total of 2 patients had a TEAE that led to infusion interruption/termination. In the EPTI300-EPTI300 group, 1 patient had *mild presyncope* that led to infusion interruption. The patient received her subsequent infusions without any adverse events. In the EPTI100-EPTI100 group, 1 patient had *mild COVID-19*, and the site reported *IMP interrupted* for the event; however, *IMP interrupted* seems to have been reported in error as it did not concern an infusion interruption, but concerned an infusion that was administered 2 weeks later than scheduled.

Safety Results (continued)

- A total of 12 patients, 3 in each of the PBO-EPTI300 and EPTI100-EPTI100 groups and 6 in the EPTI300-EPTI300 group had TEAEs leading to withdrawal. Only *pregnancy* occurred in >1 patient in any treatment group.
- 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 proportion of patients with post-Baseline PCS values across the variables were generally low and with 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.
- None of the patients had suicidal ideation or behaviour.

Immunogenicity Results

- During the entire study period (Weeks 0 to 72), the highest proportions of patients with positive ADA samples (ranging from 10% to 14% across the treatment groups) occurred 24 weeks after the first administration of eptinezumab (that is, at Week 24 in the Placebo-controlled Period and at Week 48 in the Extension Period); hereafter, the proportions declined, and at Week 72, they ranged from 1% to 4%.
- There was no indication of a relationship between the eptinezumab dose and the occurrence or titres of ADAs. No clinically relevant differences in the proportions of patients with positive NAb results were observed between the treatment groups.
- The assessment of the TEAEs in patients with positive ADA results did not indicate any safety signals related to ADA development.

Conclusions

- Statistically significant treatment effects ($p < 0.0001$) favouring eptinezumab 100 and 300 mg were seen for all the efficacy analyses included in the testing strategy.
- In the primary analysis of the primary endpoint (the mean change from Baseline in MMDs [Weeks 1-12]), both doses of eptinezumab demonstrated a clinically meaningful difference to placebo (-2.7 and -3.2 days, respectively; $p < 0.0001$).
- 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, the treatment effects were in favour of both doses of eptinezumab ($p < 0.0001$). There were clinically relevant differences in the proportions of patients who had a ≥50% or ≥75% reduction from Baseline in MMDs (Weeks 1-12). Furthermore, the difference to placebo in the change from Baseline in MMDs during Weeks 1-12 was sustained during Weeks 13-24 for both doses of eptinezumab. Finally, the patients' self-reported ability to function normally in daily life as assessed using the change from Baseline to Week 12 in the HIT-6 score was clinically relevantly greater for both doses of eptinezumab than for placebo.
- For the patients treated with eptinezumab in the Placebo-controlled Period, the improvements seen in the Placebo-controlled Period were maintained during the Extension Period for all endpoints related to eDiary-derived variables. A similar level of improvement was seen in the patients who changed treatment from placebo in the Placebo-controlled Period to eptinezumab 100 mg or 300 mg in the Extension Period.
- For the patients treated with eptinezumab in the Placebo-controlled Period, the improvements seen in the Placebo-controlled Period were maintained during the Extension Period for all secondary and exploratory endpoints. A similar level of improvement was seen in the patients who changed treatment from placebo in the Placebo-controlled Period to eptinezumab 100 mg or 300 mg in the Extension Period.
- Eptinezumab was well tolerated, supporting the benefit-risk profile of eptinezumab when administered to patients with unsuccessful prior preventive treatments. The selection criteria in this study were less restrictive than those in previous studies with eptinezumab, without new safety concerns emerging. 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 Dates
Updated Clinical Study Report (including Extension Period): 10 August 2023, original Clinical Study Report: 10 December 2021
This study was conducted in compliance with *Good Clinical Practice*.