Synopsis – Study ALD403-CLIN-015 (18903A)

Study Title

A parallel-group, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of eptinezumab administered intravenously in patients experiencing an acute attack of migraine

Investigators

47 principal investigators in 2 countries

Study Sites

42 sites in the United States and 5 sites in the country of Georgia

Publications

None (as of the date of this report)

Study Period

First patient first visit - 7 November 2019

Last patient last visit - 8 July 2020

Objectives and Endpoints

Primary Objective

To evaluate the effect of eptinezumab compared to placebo with respect to time to headache pain freedom AND time to absence of most bothersome symptom (MBS) during an intercurrent migraine that occurs in patients who are candidates for preventive therapy

Co-Primary Endpoints

- time to headache pain freedom
- time to absence of MBS

Secondary Objectives

To evaluate the efficacy of eptinezumab *vs* placebo on:

- headache pain freedom at timepoints up to 48 hours
- absence of MBS at timepoints up to 48 hours
- time to headache pain relief
- sustained headache pain freedom from 2 to 48 hours
- acute rescue medication use
- effect on symptoms of the qualifying migraine
- effect on patient-reported outcomes

Key Secondary Endpoints

- headache pain freedom at 2 hours
- absence of MBS at 2 hours

Secondary Endpoints:

- headache pain freedom at 4 hours
- absence of MBS at 4 hours
- use of rescue medication within the first 24 hours

Objectives and Endpoints (continued)	
	Exploratory Endpoints • time to headache pain relief • headache pain relief at 2 hours • headache pain relief at 4 hours • headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours • use of rescue medication within the first 48 hours • absence of photophobia at all timepoints • absence of phonophobia at all timepoints • absence of nausea at all timepoints • change from baseline in Headache Impact Test-6 (HIT-6) at Week 4 • change from baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4 • headache pain freedom at all timepoints other than 2 and 4 hours • Patient Global Impression of Change (PGIC) at Week 4 • time to next migraine • time to first rescue medication
Safety Objective To evaluate the safety of intravenous (IV) eptinezumab initiated during a migraine attack in patients who are candidates for preventive therapy	**Safety Endpoints** • adverse events and serious adverse events (SAEs) • clinical laboratory assessments • vital signs • electrocardiograms (ECGs) • Columbia-Suicide Severity Rating Scale (C-SSRS)
Study Methodology This was a parallel-group, double-blind, randomized, placebo-controlled study. Patients were randomized to receive either 100 mg eptinezumab or placebo in a 1:1 ratio. Randomization was stratified by use of concomitant migraine preventive treatment and region. The total study duration was approximately 4 to 12 weeks, including an up to 8-week screening period, with clinic visits at Screening, Day 0 (dosing day), and Week 4. Weekly site/patient contact attempts via a mobile application or phone call occurred between Screening and Day 0. The number of weekly contacts was based on the length of time from the Screening Visit to Day 0. Randomization and dosing were triggered by a qualifying migraine and occurred on Day 0. Per protocol, the investigational medicinal product (IMP) administration was initiated within 1 to 6 hours of the onset of a qualifying migraine attack. All patients were diagnosed by the investigator as having a migraine fulfilling International Classification of Headache Disorders-3 criteria prior to administration of IMP. Patients remained at the site for 4 hours after the start of infusion for observation, monitoring, and assessments. Patients were followed for 4 weeks, and longer if necessary, for safety follow-up. An electronic diary (eDiary) was assigned prior to dosing at the Day 0 visit and dosed patients completed the eDiary at the prescribed intervals through 48 hours after start of infusion (t=0). Additionally, patients completed eDiary data entry from Day 3 until a new migraine was reported.	
Number of Patients Planned Approximately 450 patients were planned for randomization.	
Diagnosis and Main Selection Criteria Men and women were eligible to participate if they were between 18 and 75 years of age, inclusive; had been diagnosed with migraine at <50 years of age; had a history of migraine for >1 year before screening; and had a	

frequency of 4 to 15 migraine days per month in the 3 months prior to screening. By history, the patient's typical migraine attack, if untreated, was associated with headache pain of *moderate* to *severe* intensity and a most bothersome symptom (MBS) of nausea, photophobia, or phonophobia. Patients were headache-free and had not used any acute or symptomatic migraine medications for at least 24 hours prior to the onset of a qualifying migraine attack.

IMP, Dose and Mode of Administration, Batch Numbers

Eptinezumab: 100 mg, as a single IV infusion in 100 mL of 0.9% saline

Lot numbers: APRF01, APSG01

Control Product, Dose and Mode of Administration, Batch Number

Placebo: given as a single IV infusion in 100 mL of 0.9% saline

Lot number: 1-FIN-3297

Duration of Treatment

This was a single-dose study with a 4-week follow-up period.

Statistical Methodology

The following analysis sets were used:

- Full analysis population (FAP): Includes all randomized patients who received eptinezumab or placebo. Patients are summarized within the treatment group to which they were randomized. This population was used for all efficacy analyses.
- Safety Population: Includes all patients who received eptinezumab or placebo. Patients are summarized within the treatment group for which they actually received treatment. This population was used for the safety analyses.

All data collected are tabulated and/or listed, as appropriate. The presentation of results may also include plots. The data from the clinical assessments are summarized by treatment group and visit using descriptive techniques.

Sample Size

Randomization of 225 patients per treatment group provided at least 90% power to detect a hazard ratio (HR) of 0.736 favouring eptinezumab at the 5% significance for both co-primary endpoints. This sample size also provided 90% power for the key secondary endpoints, assuming a response rate of 20% for the placebo group and a response rate of 34.5% for the eptinezumab group; that is, that eptinezumab increases response rates for both 2-hour endpoints by at least 14.5 percentage points, at a 5% significance level, where the correlation between the 2 endpoints was assumed to be 0.8.

Co-Primary Endpoints

In the primary analysis of each of the co-primary endpoints, the HR between eptinezumab and placebo was estimated from a Cox proportional hazards model with treatment group as effect and use of preventive migraine treatment and region as stratification factors, using Efron's method of tie handling. The stratification factors were identical to the factors used for randomization. Values were censored at the time of first use of rescue medication or at the time of last available data (up to 48 hours) in case headache pain freedom or absence of MBS, respectively, had not been obtained prior to censoring. The HR was presented with p-value and 95% confidence interval (CI).

The following sensitivity analyses were performed for each of the co-primary endpoints, using the same analysis model as for the primary analysis:

- Rescue medication: removing the rescue medication censoring
- Persistence: where an event required that it persisted for 30 minutes or longer
- 12 hours cut-off: using data up to and including the 12 hour assessments
- 4 hours cut-off: using data up to and including the 4 hour assessments

Key Secondary and Secondary Endpoints

For each of the key secondary and secondary endpoints, the treatment groups were compared using a Cochran-Mantel-Haenzel (CMH) test, adjusting for the study's stratification factors.

Testing Strategy

To show effect on the co-primary endpoints, it was required to achieve statistical significance on a 5% significance level simultaneously for both of the co-primary endpoints, and therefore no multiplicity adjustment was done. If both co-primary endpoints achieved statistical significance at a 5% significance level, the key secondary and secondary endpoints were tested hierarchically at a 5% significance level. The hierarchical testing was performed in the following order: pain freedom at 2 hours, absence of MBS at 2 hours, pain freedom at 4 hours, absence of MBS at 4 hours, use of rescue medication within 24 hours. All tests were 2-sided.

Analysis Sets and Patient Disposition

A total of 775 patients were screened. Analysis sets and patient disposition are summarized below:

	Eptinezumab 100 mg	**Placebo**	**Total**
Patients Randomized [n]	241	244	485
Patients Treated [n (%)]	238 (98.8)	242 (99.2)	480 (99.0)
Patients not Treated [n (%)]	3 (1.2)	2 (0.8)	5 (1.0)
Full Analysis Population [n (%)]	238 (98.8)	242 (99.2)	480 (99.0)
Safety Population [n (%)]	238 (98.8)	242 (99.2)	480 (99.0)

Variable [n (%)]	**Eptinezumab 100 mg (N=238)**	**Placebo (N=242)**	**Total (N=480)**
Completed infusion	230 (96.6)	236[a] (97.5)	466 (97.1)
Discontinued infusion	8 (3.4)	4 (1.7)	12 (2.5)
Completed study	235 (98.7)	241[b] (99.6)	476 (99.2)
Discontinued study early	3 (1.3)	1 (0.4)	4 (0.8)
Reason for early study discontinuation			
Lost to follow up	2 (0.8)	1 (0.4)	3 (0.6)
Adverse event	1 (0.4)	0	1 (0.2)
Patients by Visit			
Day 0	238 (100)	242 (100)	480 (100)
Week 4	235 (98.7)	240 (99.2)	475 (99.0)

[a] Two patients in the placebo group were not classified as either completing or discontinuing the infusion.

[b] One patient in the placebo group was incorrectly classified as having completed the study, but this patient did not attend the Week 4 Visit. This patient completed the 48-hour assessments and is included in the efficacy analyses.

Demographics and Baseline Characteristics of the Study Population

The treatment groups were comparable with regard to demographics and baseline migraine characteristics:

- Mean age: 44.5 years (range, 18 to 75 years); approximately 84% were women; 86% were white; 88% not Hispanic or Latino; 70% enrolled at sites in North America, 30% enrolled at sites in the country of Georgia
- Approximately 17% of patients were using concomitant migraine preventive medication

Summary of Efficacy Results

The co-primary, key secondary, and secondary efficacy results are summarized below:

Endpoint Category Endpoint	Eptinezumab 100 mg	Placebo	HR/OR (95% CI)	p-value
Co-primary				
Time to headache pain freedom, median (h)	4.0	9.0	HR=1.54 (1.20 to 1.98)	0.0006
Time to absence of MBS, median (h)	2.0	3.0	HR=1.75 (1.41 to 2.19)	<0.0001
Key secondary				
Headache pain freedom at 2 h post-dose	23.5%	12.0%	OR=2.27 (1.39 to 3.72)	0.0009
Absence of MBS at 2 h post-dose	55.5%	35.8%	OR=2.25 (1.55 to 3.25)	<0.0001
Other secondary				
Headache pain freedom at 4 h post-dose	46.6%	26.4%	OR=2.43 (1.66 to 3.56)	<0.0001
Absence of MBS at 4 h post-dose	65.1%	37.5%	OR=3.07 (2.12 to 4.46)	<0.0001
Use of rescue medication within 24 h post-dose	31.5%	59.9%	OR=0.31 (0.21 to 0.45)	<0.0001

CI = confidence interval; HR = hazard ratio; MBS = most bothersome symptom; OR = odds ratio

Statistically significant differences favouring the eptinezumab group were seen for efficacy analyses included in the testing strategy; that is, the primary, key secondary, and secondary analyses. In addition, the majority of analyses of exploratory efficacy endpoints showed differences favouring the eptinezumab group *versus* the placebo group ($p < 0.05$).

In the primary efficacy analyses, the time to headache pain freedom and the time to absence of MBS were statistically significantly shorter in the eptinezumab group *versus* the placebo group. The sensitivity analyses of the co-primary endpoints corroborated the results from the primary efficacy analysis.

The key secondary and secondary analyses of headache pain freedom and absence of MBS at 2 and 4 hours showed that the odds for improvement were statistically significantly higher in the eptinezumab group than in the placebo group. The odds for using of rescue medication within 24 hours was statistically significantly smaller in the eptinezumab group than in the placebo group.

The results of the exploratory efficacy analyses were in line with those of the primary efficacy analyses, with $p < 0.05$ for the eptinezumab group *versus* the placebo group comparisons, favouring eptinezumab. The changes from baseline to Week 4 in the HIT-6 and the PGIC at Week 4 indicate that patients in the eptinezumab group had reduced impact of headache during attacks and throughout the 4-week diary period and had improvement in the perceived impact of migraine *versus* patients in the placebo group. The changes in HIT-6 and PGIC were considered clinically relevant improvements. The change from baseline to Week 4 in the mTOQ-6 indicates that the patients in the eptinezumab group had an improved response to acute treatment *versus* patients in the placebo group.

Safety Results

The incidence of TEAEs is summarized below:

Category of event [n (%) m]	Eptinezumab 100 mg N = 238	Placebo N = 242
Any TEAE	26 (10.9) 36	25 (10.3) 31
Treatment-related TEAE	9 (3.8) 16	2 (0.8) 2
TEAE leading to withdrawal	1 (0.4)	0
TEAE leading to IMP interruption	3 (1.3) 3	2 (0.8) 3

m = number of events; n = number of patients
Adverse events were coded using MedDRA Version 20.1.

- A single 100 mg IV infusion of eptinezumab was well tolerated, and no significant safety issues were observed.
- No *fatal* or *life-threatening* TEAEs and no treatment-emergent SAEs were reported.
- One patient withdrew from the study due to an adverse event. The event was a non-serious, Grade 2 (*moderate*) upper respiratory tract infection that began on Day 32, and was assessed as *not related*.
- One TEAE preferred term (PT) was reported for 2% or more of patients in either treatment group: hypersensitivity was reported in 2.1% of patients in the eptinezumab group and in 0% of patients in the placebo group.
- The most frequent adverse event of special interest was hypersensitivity, reported for 5 patients in the eptinezumab group (all assessed as *related* to the IMP) and no patients in the placebo group. All 5 events were treatment-emergent; 3 events began during the infusion and 2 events began after the end of the infusion. One of these events was *severe* and led to interruption of the infusion. The other 4 events were *mild* or *moderate* and no action was taken with regard to the IMP. All 5 events had *resolved* at the time of reporting.
- Five patients had adverse events of special interest that led to interruption of the IMP infusion: in the eptinezumab group, 1 patient had hypersensitivity and 2 patients had infusion site extravasation; in the placebo group, 2 patients had infusion site extravasation.
- No patients had clinically meaningful changes from baseline in haematology or chemistry results, ECGs, or vital signs.

Conclusions

In the primary efficacy analysis, the time to headache pain freedom and the time to absence of MBS were statistically significantly shorter in the eptinezumab group *versus* the placebo group. The sensitivity analyses of the co-primary endpoints corroborated the results from the primary efficacy analyses.

The results of the key secondary and secondary efficacy analyses were in line with those of the primary efficacy analyses. In addition, the majority of analyses of exploratory efficacy endpoints showed differences favouring the eptinezumab group *versus* the placebo group ($p < 0.05$). Of note, the changes from baseline to Week 4 in the HIT-6 and the PGIC at Week 4 indicate that patients in the eptinezumab group had reduced impact of headache during attacks and throughout the 4-week diary period and had improvement in the perceived impact of migraine *versus* patients in the placebo group. The changes in HIT-6 and PGIC were considered clinically relevant improvements. The change from baseline to Week 4 in the mTOQ-6 indicates that the patients in the eptinezumab group had an improved response to acute treatment *versus* patients in the placebo group.

Eptinezumab was well tolerated, supporting the benefit-risk profile of eptinezumab when administered in patients having a migraine attack. The safety and tolerability profile of eptinezumab was comparable to what has been observed in previous clinical studies of eptinezumab in patients with migraine.

Report Date

25 February 2021

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