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APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #:	761119
Drug Name:	ALD403
Indication(s):	Treatment for the Prevention of [redacted] (b) (4) Migraine
Applicant:	Alder BioPharmaceuticals, Inc.
Date(s):	3/22/2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Steve Bai, Ph.D.
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Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

Eptinezumab (a.k.a ALD403) is developed by Alder BioPharmaceuticals, Inc. for the preventive treatment of migraine in adults. It is a humanized anti-calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb). The development program included two pivotal studies and administered multiple infusions of eptinezumab: episodic migraine Study ALD403-CLIN-006 and chronic migraine Study ALD403-CLIN-011. This clinical development program supporting eptinezumab has demonstrated efficacy in subjects with both episodic migraine (EM) and chronic migraine (CM).

2 INTRODUCTION

2.1 Overview

A listing of the 2 pivotal studies providing efficacy information for eptinezumab is provided in Table 2-1. These studies are placebo-controlled phase 3 studies that demonstrate the claimed effect of eptinezumab treatment on the frequency of monthly migraine days. Pivotal Study 006 enrolled subjects with episodic migraine (EM) who had received a diagnosis of migraine at $\leqslant$ 50 years of age. Pivotal Study 011 enrolled subjects with chronic migraine (CM) who had received a diagnosis of migraine at $\leqslant$ 50 years of age. In both pivotal studies, subjects received multiple IV infusions of eptinezumab given at 12-week intervals. Four infusions of eptinezumab at dose levels of either 30, 100, or 300 mg were administered in Study 006, and 2 infusions at dose levels of either 100 or 300 mg were administered in Study 011 at a frequency of once every 12 weeks. In both pivotal studies, the primary efficacy endpoint was the change from baseline in the frequency of monthly migraine days over the weeks 1-12 interval following the first dose.

Table 2-1 Listing of Eptinezumab Efficacy Studies in Patients with Migraine

Study Number	Diagnosis	Objectives of Study	Study Design and Type of Control	Number of Subjects Treated (Full Analysis Population)	Treatment Schedule	Study Duration[a]
Pivotal Studies						
006	Episodic migraine	Efficacy; Safety; PK; immunogenicity	parallel group; double-blind; placebo controlled	***4 treatment groups:*** 222 placebo 223 active (30 mg) 221 active (100 mg) 222 active (300 mg)	***4 total infusions:*** day 0 week 12 week 24 week 36	56 weeks
011	Chronic migraine	Efficacy; Safety; PK; immunogenicity	parallel group; double-blind; placebo controlled	***3 treatment groups:*** 366 placebo 356 active (100 mg) 350 active (300 mg)	***2 total infusions:*** day 0 week 12	32 weeks

In both studies enrolling subjects with episodic migraine and chronic migraine, administration of both 100-mg and 300-mg of eptinezumab by IV infusion resulted in a statistically significant, clinically meaningful migraine preventive effect across multiple efficacy measures.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room \\cdsesub1\evsprod\BLA761119\0001

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Sponsor assessed the site to verify the qualifications of each investigator, according to the Sponsor's or applicable standard operating procedures (SOPs). There was an inspection of site facilities, and the investigator was informed of responsibilities and procedures for ensuring adequate and correct documentation. The investigator was required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the clinical study for each clinical study subject. All information recorded in the eCRFs for this clinical study was consistent with the subjects' source documentation (ie, medical records).

Data for the primary and key secondary endpoints were collected in the subjects' eDiary as described in SOPs. All analyses were conducted using SAS software. Baseline assessment for migraine and headache endpoints was based upon the data recorded in the headache eDiary during the 28 days following screening. For other variables, the baseline assessment was the latest available valid measurement taken prior to the administration of the first dose of study drug.

3.2 Evaluation of Efficacy

3.2.1 ALD403-CLIN-006 STUDY EPISODIC MIGRAINES

The title of this study is *A Parallel Group Double-Blind Randomized Placebo-Controlled Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Frequent Episodic Migraines (FEM)*

The study period ranged from 30 September 2015 (First subject first visit) to 14 December 2017 (Last subject last visit). The content of this study results is based on Protocol Amendment 4 dated 24 April 2017, and the Statistical Analysis Plan (SAP) Version 1.4, dated 18 May 2017.

3.2.1.1 Study Objectives and Design

The primary objective of the study was to evaluate the efficacy of repeat doses of ALD403 administered intravenously compared to placebo in subjects with FEM.

This was a Phase 3, parallel group, double-blind, randomized, placebo-controlled study. Eligible subjects were randomly assigned into 1 of 3 ALD403 dose levels (30 mg, 100 mg, and 300 mg) or placebo in a 1:1:1:1 ratio. Randomization was stratified by migraine days during screening ($\leqslant$ 9 days versus >9 days). Subjects were allocated equally to each treatment group. The total duration of the study was 60 weeks, with 12 scheduled visits. The visits occurred at screening, on Day 0 and at Weeks 4, 8, 12, 16, 20, 24, 28, 36, 48, and 56. The 56 weeks were divided into 2

periods: a blinded analyses period of 24-week safety and efficacy period (Weeks 1-24) and a long-term safety period (Weeks 25-56).

3.2.1.2 Statistical Methodologies

Eligible subjects were randomly assigned and treated with study drug or placebo on Day 0. Subjects completed a daily headache eDiary from the time of screening through Week 48. Migraine/headache episodes were self-reported by the subject in the eDiary. An episode was defined as a single headache event that the subject reported as having a start and an end time and lasted at least 30 minutes in duration. A migraine day was any day on which the subject had a migraine or probable migraine. The primary and key secondary migraine and headache efficacy endpoints were assessed using the migraine/headache data (migraine/headache day) from the eDiary.

Efficacy Measures
The **Primary Efficacy Endpoint** is the change in frequency of migraine days (Weeks 1-12). Migraine and headache data were collected through Week 48 and were summarized in 4-week, 12-week, and 24-week intervals. Specifically, migraine and headache endpoints were summarized for the following 4-week intervals: Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, and so on up to Weeks 44-48. The 12-week intervals were Weeks 1-12, 13-24, 25-36, and 37-48, and the 24-week intervals were Weeks 1-24 and 25-48. The results from Weeks 1-12 were used for the primary analysis.

The frequency of migraine days is the number of migraine days within 4-week intervals and the average 4-week frequency in 12-week intervals. Change from baseline is the difference in frequency between baseline and the counts within these 4-week intervals. The 12-week change is the difference in the frequency between baseline and the average of the 4-week intervals.

The **key secondary endpoints** were the following:
- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)
- 50% migraine responder rate (Weeks 1-12)
- Percentage of subjects with a migraine on the day after dosing.

Three responder rates were defined: 50% and 75%. A responder was a subject who achieved a $\geqslant$ 50% reduction or $\geqslant$75% reduction in migraine days, respectively. These reductions were evaluated by comparing the baseline frequency of migraine days to the migraine frequency in 4-week intervals.

Analysis Population
The population to be analyzed is Full Analysis Population, which included randomized subjects who received Investigational Product/placebo.

Determination of Sample Size
The planned sample size for this study is 800 subjects. These subjects will be allocated into 4 treatment groups in a 1:1:1:1 ratio. Pair-wise testing of each ALD403 group vs. placebo will be performed. Two hundred subjects per group provides at least 95% power for each change in

frequency of migraine days (Weeks 1-12) test individually assuming a treatment effect of at least 1 day and a common standard deviation of 2.7 days or less. At the end of the study, approximately 900 subjects were to be assigned to 4 treatment groups.

Primary Efficacy Analyses

The primary endpoint is the change from baseline in migraine days from Weeks 1-12. The hypotheses tested are

$$H_0: \Delta_{plb} = \Delta_{403} \text{ vs. } H_a: \Delta_{plb} \neq \Delta_{403}$$

where Δ_{403} is the change in migraine days for subjects in the ALD403 treatment arm and Δ_{plb} is similarly defined for the placebo subjects. An ANCOVA model was used to test for a difference between treatment arms. This model included the change from baseline measure as the response variable.

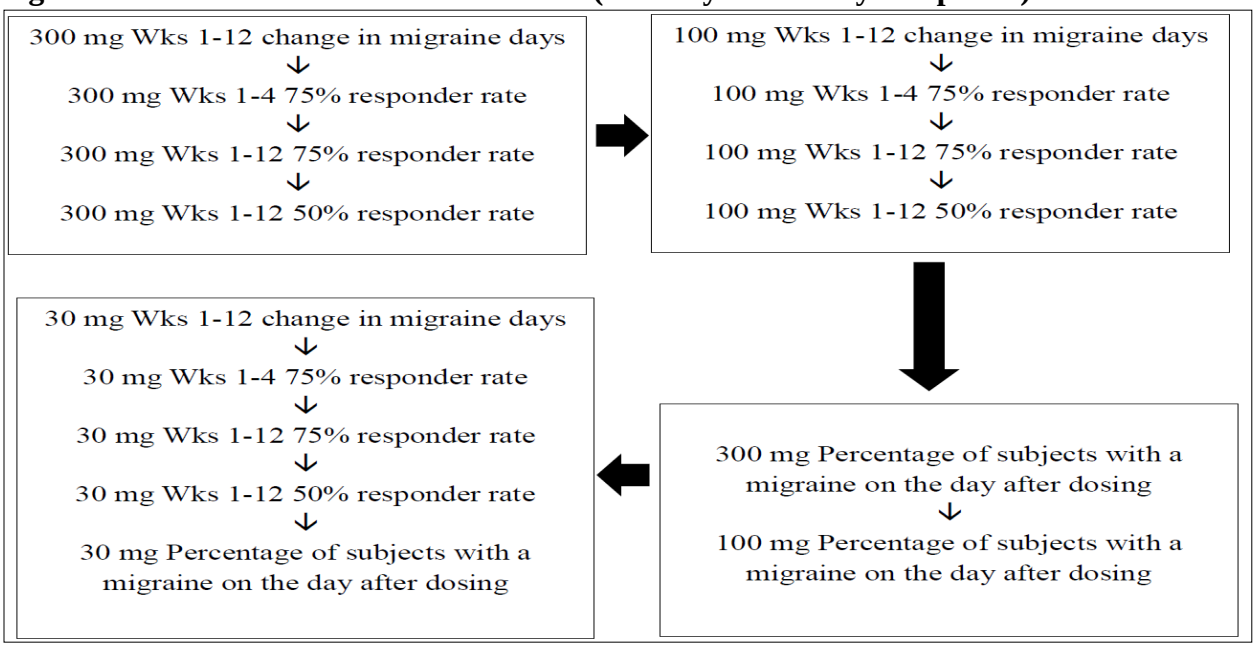
Secondary Efficacy Analyses

For the key secondary endpoints (responder rates and percentage of subjects with a migraine on the day after dosing) this testing will utilize a CMH/extended CMH test. The tests will be stratified by the randomization stratification factor.

Multiple Comparisons/Multiplicity

A serial procedure was used to account for multiplicity of dose level for the primary endpoint and the secondary endpoints (Figure 3-1).

Figure 3-1 Decision Rule for Dose levels (Primary/Secondary Endpoints)



This procedure started with the 300 mg vs placebo comparison for the primary endpoint. If this is significant, testing will continue to a subset of the key secondary endpoints for 300 mg (first the Weeks 1-4 75% responder endpoint, then the Weeks 1-12 75% responder endpoint, and then the Weeks 1-12 50% responder endpoint). The procedure will then move on to the primary endpoint for the 100 mg group and subsequently to the same subset of key secondary endpoints as tested

for the 300 mg dose. The procedure will then move on to the remaining key secondary endpoint for 300 mg and 100 mg (i.e., percentage of subjects with a migraine on the day after dosing). Only if all these secondary endpoints reach statistical significance will the 30 mg group be tested.

Approaches for Handling Missing Data
If the end date and time for a headache recorded in the eDiary was missing, the headache end date was set to the earlier of 23:59 on the day before the next reported headache or 23:59 on the last entry reported into the eDiary (ie, the last evening report or if no evening report was completed after the start of the headache, 23:59 on the day the headache started). Headaches that were not reported as stopped by the subject did not have the answers to the questions that allowed for the determination of whether the headache was a migraine or not.

Missing Data Rule 1: If the eDiary was completed for at least 21 days in a 28-day interval, a normalization procedure was used whereby the results were normalized to 28 days by multiplying the observed results by the inverse of the completion rate (e.g., if a subject did not complete the eDiary for 5 days they were considered to have completed the eDiary on 82% of the days and the normalized results were calculated as the observed results times 1.22).

Missing Data Rule 2: If the eDiary was completed for less than 21 days in the 28-day interval, the results for the28-day interval were a weighted function of the observed data for the current 4-week interval and the results from the previous interval. The weights were proportional to the number of days the eDiary was completed and provided greater weight for higher completion rates. Specifically, the results were derived as follows: 28*(W* Xc + (1 - W)* Xp), where W was the number of days the eDiary was completed/20, Xc was the available average daily results for the current interval, and Xp was the average imputed daily results for the previous interval.

Sensitivity Analysis
Several sensitivity analyses were performed. The first group of sensitivity analyses implemented the missing data rules as follows:

- The primary endpoint was analyzed using a modification to the Missing Date Rule 2 (eDiary completed for fewer than 21 days) to better understand the robustness of the selected algorithm. The analysis replaces Xp with Xb, where Xb were the baseline average daily results, if the subject withdrew from the study due to an AE, study burden, lack of efficacy, or worsening of study indication, or if the subject died.
- The primary endpoint was analyzed using repeated measures where the individual time periods (Weeks 1-4, 5-8, and 9-12) were included in the model and Missing Date Rule 2 (eDiary completed for fewer than 21 days) was not used; hence, subjects who did not complete the diary for more than 7 days out of 28 were not included for that 4-week period. The model specified an unstructured variance/covariance matrix and included the treatment group, timepoint, baseline, and treatment group-by-timepoint interaction.

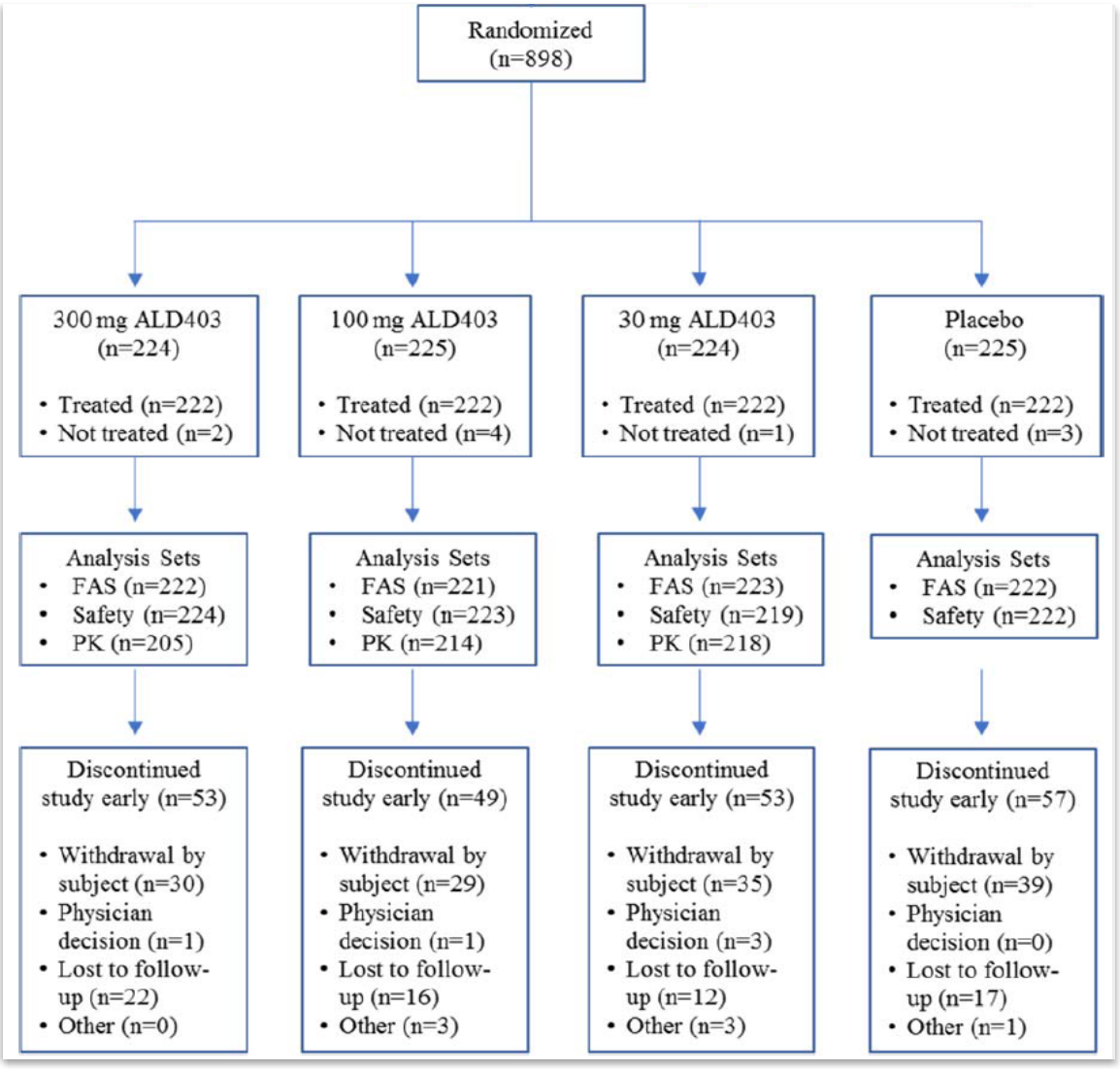
The second group of sensitivity analyses changed the definition of baseline. Baseline was redefined using 28 days of headache diary data ending on the day of the first dose. The primary analysis was repeated using this updated definition of the baseline.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Disposition of Subjects

Figure 3-2 summarized subject disposition. Of 898 subjects who were randomized, 10 were not treated; of these, 2 subjects did not meet the eligibility criteria but were randomized in error, 4 subjects withdrew consent due to study burden and/or difficulty with IV placement for infusion, 1 subject had a positive urine pregnancy test on Day 0, 1 subject was not dosed because there was no study drug at the study site and 2 subjects did not provide specific reasons.

Figure 3-2 Subject Disposition



[*Note:page 74 of the sponsor's study report*]

Demographic and Baseline Characteristics

Table 3-1 summarized demographics and baseline characteristics. Overall, subject demographics across treatment groups were generally well balanced and any minor differences observed were

not considered to be clinically relevant. The mean age was 39.8 years. Most of the subjects were females, the majority were not of Hispanic or Latino ethnicity and the majority were racially identified as white.

Table 3-1 Demographics and Baseline Characteristics

Status	ALD403 300 mg N = 224	ALD403 100 mg N = 223	ALD403 30 mg N = 219	Placebo N = 222	Overall N = 888
Age (years)					
n	224	223	219	222	888
Mean (SD)	40.2 (11.72)	40.0 (10.66)	39.1 (11.54)	39.9 (11.67)	39.8 (11.39)
Median	40.0	40.0	37.0	39.5	39.0
Min, Max	18, 71	18, 68	18, 69	20, 68	18, 71
Age Group, n (%)					
≤35 years	89 (39.7)	73 (32.7)	93 (42.5)	88 (39.6)	343 (38.6)
>35 years	135 (60.3)	150 (67.3)	126 (57.5)	134 (60.4)	545 (61.4)
Sex, n (%)					
Male	25 (11.2)	44 (19.7)	34 (15.5)	36 (16.2)	139 (15.7)
Female	199 (88.8)	179 (80.3)	185 (84.5)	186 (83.8)	749 (84.3)
Ethnicity, n (%)					
Hispanic or Latino	40 (17.9)	42 (18.8)	45 (20.5)	34 (15.3)	161 (18.1)
Not Hispanic or Latino	184 (82.1)	181 (81.2)	174 (79.5)	188 (84.7)	727 (81.9)
Race, n (%)					
White	187 (83.5)	196 (87.9)	180 (82.2)	181 (81.5)	744 (83.8)
Black or African American	27 (12.1)	17 (7.6)	31 (14.2)	30 (13.5)	105 (11.8)
Asian	1 (<1)	1 (<1)	1 (<1)	2 (<1)	5 (<1)
American Indian or Alaska Native	2 (<1)	0	0	1 (<1)	3 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	0	1 (<1)	3 (<1)
Multiple Races	5 (2.2)	7 (3.1)	5 (2.3)	5 (2.3)	22 (2.5)
Other	1 (<1)	1 (<1)	2 (<1)	2 (<1)	6 (<1)

[*Note: copied from page 80 of the sponsor's study report*]

Table 3-2 presents a summary of eDiary-reported baseline migraine and headache characteristics. Overall, the migraine and headache characteristics were similar across treatment groups at baseline and minor differences observed were not considered to be clinically relevant. The mean number of baseline migraine days and baseline headache days were similar across the treatment groups. The mean baseline number of migraine attacks and headache episodes were similar

across treatment groups. The mean baseline migraine hours ranged from 76.0 to 84.5 hours, and mean baseline headache hours ranged from 83.6 to 92.7 hours.

Table 3-2 Baseline Migraine and Headache Characteristics

eDiary-Reported Characteristic [a]	ALD403 300 mg N = 222	ALD403 100 mg N = 221	ALD403 30 mg N = 223	Placebo N = 222
Baseline migraine days				
Mean (SD)	8.6 (2.87)	8.7 (2.85)	8.7 (3.05)	8.4 (2.68)
Baseline headache days				
Mean (SD)	10.1 (3.06)	10.0 (3.02)	10.2 (3.35)	9.9 (2.83)
Baseline migraine attacks				
Mean (SD)	6.2 (2.26)	6.4 (2.19)	6.4 (2.53)	6.4 (2.27)
Baseline headache episodes				
Mean (SD)	7.6 (2.81)	7.7 (2.68)	8.0 (3.16)	8.0 (2.67)
Baseline migraine hours				
Mean (SD)	84.5 (55.42)	80.8 (51.76)	80.7 (54.24)	76.0 (44.64)
Baseline headache hours				
Mean (SD)	92.7 (58.62)	86.8 (53.44)	88.5 (57.19)	83.6 (46.91)
Baseline percent of migraines with severe intensity				
Mean (SD)	28.21 (25.410)	33.89 (28.635)	35.70 (30.332)	33.61 (28.478)
Baseline average length in hours of migraine attack				
Mean (SD)	15.34 (12.486)	13.83 (11.846)	14.05 (13.057)	12.87 (9.961)

[Note: This table was copied from page 86 of the sponsor's study report.]

3.2.1.4 Efficacy Results and Conclusions

Based on the decision rule of Figure 3-1, the results for the primary endpoint and key secondary endpoints for the ALD403 300-mg group were statistically significant. The primary endpoint and 75% migraine responder rate over Weeks 1-4 were statistically significant for the ALD403 100-

mg dose. However, the 75% migraine responder rate over Weeks 1-12 was not statistically significant. The decision rules stopped the testing of all remaining endpoints.

Primary Efficacy Endpoint

This primary efficacy endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of migraine days over Weeks 1-12.

Table 3-3 Analysis of Migraine Days by 12-Week Interval (FAS)

Parameters	ALD403 300 mg	ALD403 100 mg	ALD403 30 mg	Placebo
N	222	221	223	222
Mean Change from Baseline	-4.29	-3.88	-4.01	-3.19
Mean Diff from Placebo	-1.11	-0.69	-0.82	
95% CI	(-1.68, -0.54)	(-1.25, -0.12)	(-1.39, -0.25)	
p-value	0.0001	0.0181	0.0046	
Decision	S	S	NS	
Simple Mean Change from Baseline	-4.3	-3.7	-4.3	-3.3
Simple Mean Diff from Placebo	-1.3	-0.9	-1.0	
95% CI	(-1.91, -0.59)	(-1.5, -0.2)	(-1.64, -0.35)	

Abbreviations: NS = nominally significant; S = significant

Figure 3-3 CDF of Change from Baseline Migraine Days for Weeks 1-12 (FAS)

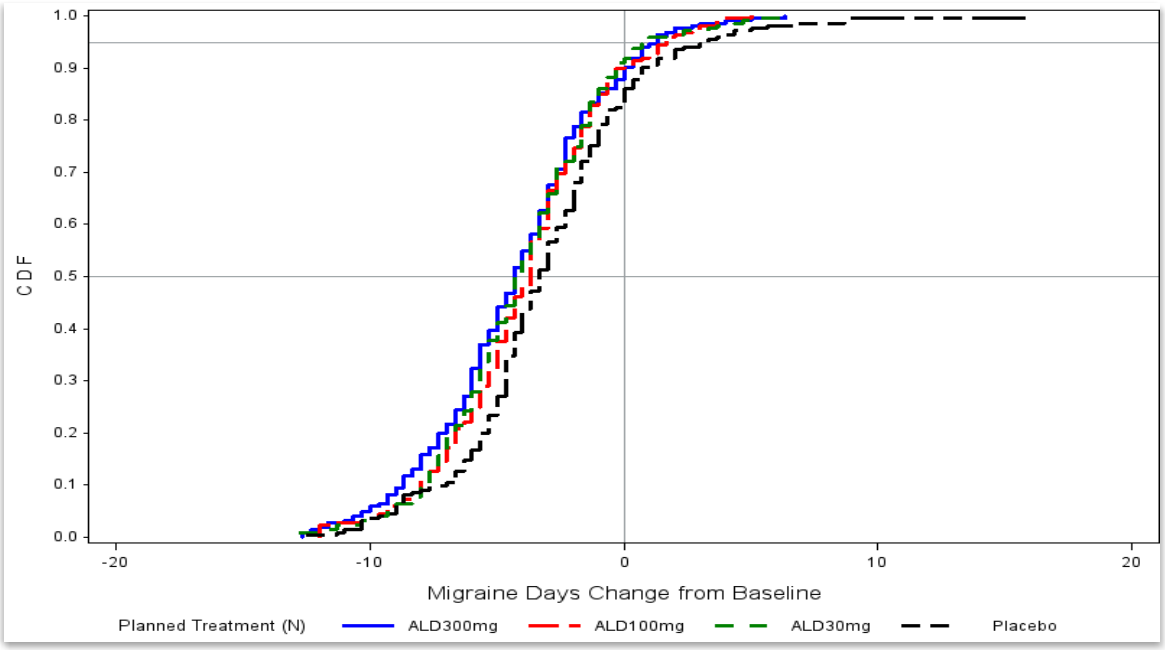


Table 3-3 presents an analysis of migraine days by 12-week interval and treatment. With a mean difference of -1.11 days (95% CI: -1.68, -0.54), the ALD403 300-mg dose demonstrated a statistically significant improvement (P=0.0001) from placebo. The ALD403 100-mg dose demonstrated a statistically significant (P=0.0182) improvement from placebo with a mean

difference of -0.69 days (95% CI: -1.25, -0.12) for Weeks 1-12. Based on the multiplicity decision rule (Figure 3-1), the results for the study's primary efficacy endpoint was statistically significant in the ALD403 300-mg and 100-mg groups compared to placebo. The ALD403 30-mg group was nominally significant (P=0.0046) from placebo with a mean difference of -0.82 days (95% CI: -1.39, -0.25). The similar results are obtained when the change from baseline is the difference in simple average migraine days between baseline and the Weeks 1-12 interval.

Error! Reference source not found. presents the cumulative distribution function (CDF) of change from baseline migraine days for Weeks 1-12.

Handling of Dropouts and Sensitivity Analysis

Nearly all subjects remained in the study through Week 12 with fewer than 10 subjects (<5%) in the 300-mg and 100-mg groups not attending the Week 12 visits and 17 placebo subjects not attending the Week 12 visit, see Table 3-4.

Table 3-4 Subjects Dropouts by through Week 12

Subjects by Visits	ALD403 300 mg	ALD403 100 mg	ALD403 30 mg	Placebo
Day 0	222	221	223	222
Week 12	213	212	205	205

Results of the sensitivity analyses based upon a modified missing data imputation rule (imputing baseline migraine days for subject who withdrew due to AEs, study burden or lack of efficacy) and modified definition of baseline (baseline is the 28 days prior to the first treatment instead of the first 28 days of screening) support the primary efficacy endpoint analysis. In these analyses, the upper limit of the confidence interval remains below zero demonstrating greater changes from baseline in the ALD403 groups compared with the placebo group. These results established the robustness and internal consistency of the treatment effects of the 300-mg and 100-mg dose groups compared to placebo.

Table 3-5 Sensitivity Analyses of Migraine Days by 12 Week Intervals

	ALD403 300 mg	ALD403 100 mg	ALD403 30 mg
[a]Mean Diff from Placebo (95% CI)	-1.2 (-1.91, -0.58)	-0.9 (-1.53, -0.23)	-1.0 (-1.65, -0.36)
[b]Mean Diff from Placebo (95% CI)	-1.2 (-1.75, -0.60)	-0.7 (-1.23, -0.09)	-0.8 (-1.38, -0.24)

[a] uses baseline results if a subject withdrew from the study due to an adverse event, study burden, lack of efficacy or death.

[b] uses the definition of baseline as the 28 days prior to treatment start date. Missing eDiary data is handled using the rules provided in SAP.

Key Secondary Efficacy Endpoints

Table 3-6 summarized the 75% migraine responder rate compared to placebo over Weeks 1-4 and Weeks 1-12, and 50% migraine responder rate compared to placebo for Weeks 1-12.

The 75% migraine responder rate over Weeks 1-4 demonstrated a statistically significant improvement for the ALD403 300 mg and ALD403 100 mg group over placebo. The ALD403 30 mg only reached the nominal statistical significance vs. placebo, per the multiplicity decision rule.

The 75% migraine responder rate over Weeks 1-12 demonstrated a statistically significant improvement (P=0.0007) for ALD403 300 mg over placebo group. The ALD403 100mg was not statistically significant vs. placebo. The treatment effect for 30 mg group was nominally significant vs. placebo, per the multiplicity rule.

The 50% migraine responder rate over Weeks 1-12 demonstrated a statistically significant improvement for ALD403 300 mg over placebo group. The ALD403 100mg and 30mg were both nominally significant vs. placebo, per the multiplicity decision rule.

Table 3-6 Summary of Different Migraine Responder Rates (FAS)

Time Interval	ALD403 300 mg N=222	ALD403 100 mg N=221	ALD403 30 mg N=223	Placebo N=222
Weeks 1-4				
75% Responder (%)	70 (31.5)	68 (30.8)	67 (30.0)	45 (20.3)
Diff vs. Placebo (95% CI)	11.3 (3.2, 19.3)	10.5 (2.4, 18.6)	9.8 (1.8, 17.8)	
OR vs. Placebo (95% CI)	1.82 (1.18, 2.80)	1.75 (1.13, 2.71)	1.69 (1.10, 2.62)	
p-value[a]	0.006	0.0112	0.017	
Decision	S	S	NS	
Weeks 1-12				
75% Responder (%)	66 (29.7)	49 (22.2)	55 (24.7)	36 (16.2)
Diff vs. Placebo (95% CI)	13.5 (5.8, 21.2)	6.0 (-1.4, 13.3)	8.4 (1.0, 15.9)	
OR vs. Placebo (95% CI)	2.18 (1.38, 3.44)	1.47 (0.91, 2.37)	1.69 (1.06, 2.69)	
p-value[a]	0.0007	0.113	0.027	
Decision	S	*	NS	
Weeks 1-12				
50% Responder (%)	125 (56.3)	110 (49.8)	112 (50.2)	83 (37.4)
Diff vs. Placebo (95% CI)	18.9 (9.8, 28.0)	12.4 (3.2, 21.5)	12.8 (3.7, 22.0)	
OR vs. Placebo (95% CI)	2.16 (1.48, 3.16)	1.66 (1.14, 2.43)	1.69 (1.16, 2.47)	
p-value[a]	0.0001	0.0085	0.0064	
Decision	S	NS	NS	

*Abbreviations: NS = nominally significant; S = significant; * = not significant*
[a] p-values obtained from CMH test

The percentage of subjects with a migraine on the day after dosing (Day 1) decreased in the ALD403 300 mg and 100 mg groups, respectively. When compared with placebo, the percentage of subjects with a migraine on the day after dosing (Day 1) in the ALD403 300 mg and 100 mg groups were both nominally significantly lower (per the decision rule) than the placebo group, see Table 3-7.

Table 3-7 Summary of Percentages of Subjects with Migraine from Baseline to Day 1

Assessment	ALD403 300 mg N=222	ALD403 100 mg N=221	ALD403 30 mg N=223	Placebo N=222
Percentage of Subjects with a Migraine				
Baseline[a]	30.8	31.0	31.0	29.8
Day 0[b]	18.5	19.4	19.9	20.5
Day 1	13.9	14.8	17.3	22.5
p-value[c]	0.0159	0.0312	0.1539	

Statistical Significance of Efficacy Endpoints
Based on the decision rule outlined in Figure 3-1:

- The results for the primary endpoint, (the change in frequency of migraine days for Weeks 1-12), and key secondary endpoints (such as 75% migraine responder rate over Weeks 1-4), 75% and 50% migraine responder rates over Weeks 1-12 for the ALD403 300-mg group were statistically significant.
- The primary endpoint and 75% migraine responder rate over Weeks 1-4 were statistically significant for the ALD403 100-mg dose; however, the 75% migraine responder rate over Weeks 1-12 was not statistically significant.
- The remaining key secondary endpoints in the ALD403 300-mg and 100-mg groups were not statistically significant despite unadjusted p-values being <5%, due to the decision rules of multiple testing.

3.2.2 ALD403-CLIN-011 STUDY CHRONIC MIGRAINE

Title of Study: *A Parallel Group, Double-Blind, Randomized, Placebo Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine*.

The study period ranged from 30 September 2015 (First subject first visit) to 14 December 2017 (Last subject last visit). The content of this study report is based on Protocol Amendment 3 dated 31 Aug 2017, and the Statistical Analysis Plan (SAP) Version 1.0, dated 08 November 2017.

3.2.2.1 Study Objectives and Design

The primary objective of the study was to evaluate the efficacy of repeat doses of ALD403 administered IV compared to placebo in subjects with chronic migraine.

This was a Phase 3, parallel group, double-blind, randomized, placebo-controlled study. Eligible subjects were randomly assigned 28 to 30 days after the screening visit into 1 of 2 ALD403 dose levels (100 mg or 300 mg) or placebo in a 1:1:1 ratio. Randomization was stratified by baseline migraine days (<17 days versus ⩾17 days during screening) and prophylactic medication use during the 3 months before screening (prophylactic medication uses vs. no prophylactic medication use). The study participation period was approximately 36 weeks, including the

screening period. The scheduled visits occurred at screening, randomization (on-site or phone), Day 0, and Weeks 2, 4, 8, 12, 16, 20, 24, and 32. Subjects completed the eDiary daily through Week 24.

3.2.2.2 Statistical Methodologies

Subjects will complete a daily headache eDiary from the time of screening to Week 24. It is these headache reports which are used to derive the migraine and headache endpoints. Headaches (i.e. headache episodes) will be self-reported by the subject. An episode is a single headache event which lasts at least 30 minutes, as defined by the subject reported start and end time. The migraine and headache endpoints will be summarized in four-week, twelve week and the twenty-four-week intervals. A migraine day is defined as any day with a headache that meets the chronic migraine definition as outlined in the International Headache Society (IHS) International Classification of Headache Disorders.

Efficacy Measures
The **Primary Efficacy Endpoint** is the change in frequency of migraine days (Weeks 1-12). A migraine day is defined as any day with a headache that meets the chronic migraine definition as outlined in the International Headache Society (IHS) International Classification of Headache Disorders. The frequency of migraine days is the number of migraine days within four-week intervals and the average four-week frequency in twelve- and twenty-four-week intervals. Change from baseline is the difference in frequency between baseline and the counts witin these four-week intervals. The 12- and 24-week change is the difference in the frequency between baseline and the average of the 4-week intervals.

The **key secondary endpoints** were the following:

- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)
- 50% migraine responder rate (Weeks 1-12)
- Percentage of subjects with a migraine on the day after dosing.
- Reduction in migraine prevalence from baseline to Week 4
- Headache Impact Test (HIT-6)
- Acute Migraine Medication Usage (Weeks 1-12)

Migraine/ Headache Responder Rate
A responder is a subject who achieves a $\geqslant$50% reduction, or $\geqslant$75% reduction in migraine days, respectively. These reductions will be evaluated by comparing the baseline frequency of migraine days to the migraine frequency in four-week intervals. Results from the four-week intervals will be averaged to produce 12- and 24-week responder endpoints.

Reduction in Migraine Prevalence from Baseline to Week 4
The average percent of subjects with a migraine on any given day during baseline and the equivalent rate over Weeks 1, 2, 3 and 4 will be evaluated for the treatment arms. These treatment arm rates will be based upon subject rates. The baseline daily rate for a subject will be calculated as the number of migraine days within baseline for that subject divided by 28. The treatment (e.g. 300 mg) average baseline prevalence is calculated as the average of the subject

level rates for baseline. The weekly (i.e. Weeks 1, 2, 3 and 4) subject level rates will be the number of migraine days within the week divided by 7. The difference in rates between these weeks and baseline will be subject level reduction in migraine prevalence which will be averaged to produce treatment level reduction in daily migraine prevalence.

Acute Migraine Medication Usage
The number of days that subjects used acute migraine medication (i.e. triptan or ergotamine) will be summarized in 4, 12, and 24-week intervals. The 12- and 24-week results will be the average of the individual 4-week results that make up those wider intervals (e.g. the secondary endpoint of Weeks 1-12 will be the average of the Weeks 1-4, 5-8, and 9-12 results). The change from baseline for these measures will be the difference between the post baseline interval and baseline.

Headache Impact Test (HIT-6 v1.0)
The Headache Impact Test (HIT) is a tool used to measure the impact and effect on the ability to function normal in daily life when a headache occurs. The HIT is a 6 question, Likert-type, self-reporting questionnaire with responses ranging from “Never” to “Always” with the following response scores: Never=6, Rarely=8, Sometimes=10, Very Often=11, Always=13. The total score for the HIT is the sum of each response score and will be treated as missing if the response is missing for one or more questions. The HIT total score ranges from 36 to 78, with score ranges having the following life impact:

Score Range	Life Impact
>= 60	Severe
56-59	Substantial
50-55	Some
<= 49	Little to None

Populations Analyzed
The analysis populations are defined as the following:

- Full Analysis Population (FAP) – Randomized subjects who received Investigational Product/placebo. This population will be used for all efficacy analyses.
- Safety Population – Includes all subjects who received Investigational Product/placebo. Subjects will be summarized within the treatment group for which they actually received treatment. If a subject is treated with two different doses they will be summarized in treatment arm of the highest dose received. This population will be used for the safety analyses.

Determination of Sample Size
The planned sample size for this study is 1050 randomized and treated subjects. These subjects will be allocated into 3 treatment groups in a 1:1:1 ratio. Pair-wise testing of each ALD403 group vs. placebo will be performed. Three hundred and fifty subjects per group provides at least 90% power for the primary endpoint for each comparison assuming a treatment effect of at least 1 day and a common standard deviation of 4 days or less. For the key secondary 75% responder rate endpoints 90% power is achieved for the pair-wise comparisons, assuming a placebo responder rate of 20%, and an ALD403 rate of 31%.

Primary Efficacy Analysis
Hypothesis testing was performed for the primary endpoint: change in frequency of migraine days (Weeks 1-12). The hypotheses tested are

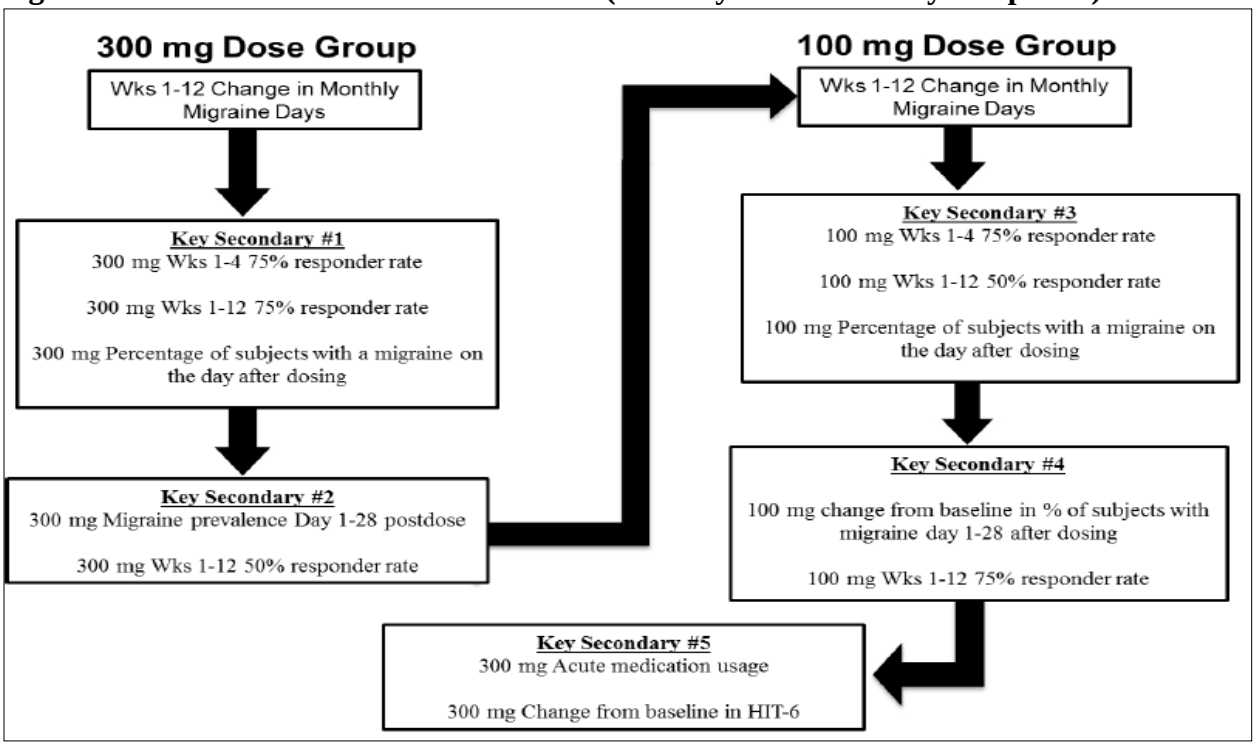
$$H_0: \Delta_{plb} = \Delta_{403} \text{ vs. } H_a: \Delta_{plb} \neq \Delta_{403}$$

where Δ_{403} is the change in migraine days for subjects in the ALD403 treatment arm and Δ_{plb} is similarly defined for the placebo subjects. An ANCOVA model was used to test for a difference between treatment arms. This model included the change from baseline measure as the response variable. Treatment and variables measuring the stratification factors concepts, baseline migraine days (continuous covariate), and prophylactic medication use (binary covariate: use versus no use) were the independent variables.

Key Secondary Efficacy Analyses
- *Responder Rates*: Testing of the migraine responder rate endpoints was performed with a CMH test controlling for the randomization stratification factors baseline migraine days (<17 days, ⩾17 days) and prophylactic medication use (use versus no use).
- *Percentage of Subjects with a Migraine on the Day after Dosing*: stratified extended CMH test. Randomization stratification factors baseline migraine days (<17 days, ⩾17 days) and prophylactic medication use (use versus no use) were used for this test.
- *Reduction in Migraine Prevalence from Baseline to Week 4*: The treatment effect was tested using a repeated-measures approach using the subject level change in migraine rate for Weeks 1, 2, 3 and 4 as the outcome variable. The model specified an unstructured variance/covariance matrix and included the treatment group, week, baseline value of the outcome variable and with treatment group-by-week interaction.
- *Headache Impact Test (HIT-6)*: The change in HIT-6 total score will be tested using an ANCOVA model similar to the one used for the primary endpoint.
- *Acute Migraine Medication Usage*: The change in acute migraine medication usage between baseline and Weeks 1-12 will be tested using an ANCOVA model similar to the one used for the primary endpoint.

Multiple Comparisons/Decision Rule
A multiplicity procedure was used to account for multiplicity associated with more than 1 dose level and for the multiple endpoints. A combination of gate keeping and the Holm's procedure will be used to control the study wide Type-I error rate. At a high level this procedure will start with the 300 mg vs placebo comparison for the primary endpoint. If this is significant, testing will continue to the first group of key secondary endpoints for 300 mg where Holm's multiplicity procedure will be used. Testing will then continue to the second group of key secondary endpoints and then move on to the 100 mg group for the primary endpoint and subsequently the key secondary endpoints using the same methodology (Holm's within each group). If these endpoints were significant, the procedure moved to the final secondary endpoints for 300 mg. Within each endpoint group, Holm's procedure was used. The testing sequence is presented in Figure 3-4.

Figure 3-4 Decision Rule for Dose Levels (Primary and Secondary Endpoints)



Greater detail concerning the groups of secondary endpoints and Holm's testing algorithm is provided in Table 3-8.

Table 3-8 Key Efficacy Analyses and Multiplicity Adjustment

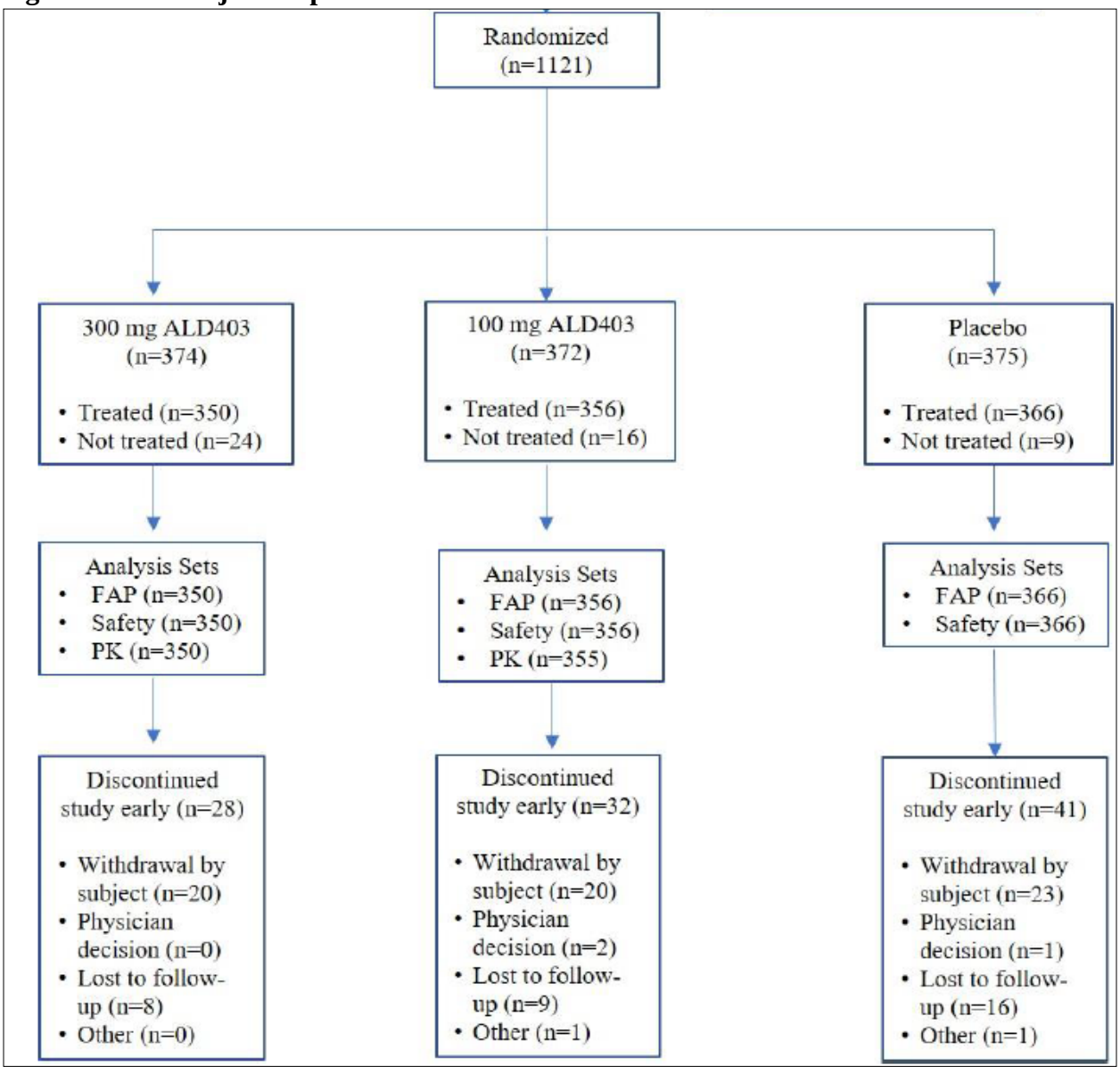
Testing Sequence	Endpoint	Population	Declare Significant
Key Secondary #1	300 mg Wk1-4 75% responder rate	FAP	$p_{(1)} < 0.0167$ $p_{(2)} < 0.025$ $p_{(3)} < 0.05$
	300 mg Wk1-12 75% responder rate	FAP	
	300 mg % subjects with migraine on the day after dosing	FAP	
Key Secondary #2	300 mg migraine prevalence Day 1-28 Post dose	FAP	$p_{(1)} < 0.025$ $p_{(2)} < 0.05$
	300 mg wk 1-12 50% responder rate	FAP	
Key Secondary #3	100 mg Wk1-4 75% responder rate	FAP	$p_{(1)} < 0.0167$ $p_{(2)} < 0.025$ $p_{(3)} < 0.05$
	100 mg Wk1-12 50% responder rate	FAP	
	100 mg % subjects with migraine on the day after dosing	FAP	
Key Secondary #4	100 mg migraine prevalence Day 1-28 Post dose	FAP	$p_{(1)} < 0.025$ $p_{(2)} < 0.05$
	100 mg wk 1-12 75% responder rate	FAP	
Key Secondary #5	300 mg Acute medication usage	FAP	$p_{(1)} < 0.025$ $p_{(2)} < 0.05$
	300 mg Change from baseline in HIT-6	FAP	

Approaches for Handling Missing Data/Sensitivity Analyses
The missing data and sensitivity analyses were handled similarly as described for study ALD403-Clin-006, see Section 3.2.1.2.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Disposition of Subjects
Of the 1121 subjects who were randomized, 49 subjects (4.4%) were not treated. The most frequently reported reasons for early study discontinuation were withdrawal by subject (63 subjects [5.9%]) and lost to follow-up (33 subjects [3.1%]), see Figure 3-5.

Figure 3-5 Subject Disposition



[*Note: copied from page 77 of the sponsor's study report*]

Demographics

Overall, subject demographics across groups were generally well balanced and any minor differences observed were not considered to be clinically relevant. The mean age was 40.5 years and most subjects (704 [65.7%]) were in the > 35-years age group. The majority of subjects were females (88.2%), most were not of Hispanic or Latino ethnicity (986 subjects [92.0%]), and most were racially identified as white (975 subjects [91.0%]), see Table 3-9.

Table 3-9 Demographics and Baseline Characteristics

Status	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366	Overall N=1072
Age (years)				
n	350	356	366	1072
Mean (SD)	41.0 (10.36)	41.0 (11.72)	39.6 (11.28)	40.5 (11.15)
Median	40.5	41.0	40.0	41.0
Min, max	18, 65	18, 65	18, 65	18, 65
Age Group, n (%)				
≤ 35 years	114 (32.6)	113 (31.7)	141 (38.5)	368 (34.3)
> 35 years	236 (67.4)	243 (68.3)	225 (61.5)	704 (65.7)
Sex, n (%)				
Male	36 (10.3)	49 (13.8)	41 (11.2)	126 (11.8)
Female	314 (89.7)	307 (86.2)	325 (88.8)	946 (88.2)
Ethnicity, n (%)				
Hispanic or Latino	18 (5.1)	33 (9.3)	35 (9.6)	86 (8.0)
Not Hispanic or Latino	332 (94.9)	323 (90.7)	331 (90.4)	986 (92.0)
Race, n (%)				
White	322 (92.0)	332 (93.3)	321 (87.7)	975 (91.0)
Black or African American	23 (6.6)	21 (5.9)	38 (10.4)	82 (7.6)
Asian	1 (< 1)	1 (< 1)	1 (< 1)	3 (< 1)
American Indian or Alaska Native	1 (< 1)	1 (< 1)	1 (< 1)	3 (< 1)
Native Hawaiian or other Pacific Islander	1 (< 1)	0	0	1 (< 1)
Multiple Races	2 (< 1)	1 (< 1)	4 (1.1)	7 (< 1)
Other	0	0	1 (< 1)	1 (< 1)
Region, n (%)				
European Union	53 (15.1)	50 (14.0)	51 (13.9)	154 (14.4)
North America	195 (55.7)	198 (55.6)	232 (63.4)	625 (58.3)
Other	102 (29.1)	108 (30.3)	83 (22.7)	293 (27.3)

[*Note: copied from page 83 of the sponsor's study report*]

Table 3-10 presented a summary of eDiary-reported baseline migraine characteristics. Overall, the migraine and headache characteristics were similar across groups at baseline. The mean number of baseline migraine days and baseline headache days were similar across the groups (ranging from 16.1 to 16.2 migraine days and 20.4 to 20.6 headache days). The mean baseline number of migraine attacks and headache episodes were similar across groups. The mean baseline migraine hours ranged from 170.8 to 177.4 hours, and mean baseline headache hours ranged from 199.5 to 210.3 hours.

Table 3-10 eDiary-Reported Baseline Migraine Characteristics

eDiary-Reported Characteristic [a]	ALD403 300 mg N = 350	ALD403 100 mg N = 356	Placebo N = 366
Baseline migraine days			
Mean (SD)	16.1 (4.77)	16.1 (4.61)	16.2 (4.55)
Baseline headache days			
Mean (SD)	20.4 (3.22)	20.4 (3.10)	20.6 (2.99)
Baseline migraine attacks			
Mean (SD)	12.1 (5.30)	12.0 (5.13)	11.6 (4.88)
Baseline headache episodes			
Mean (SD)	16.8 (6.14)	16.7 (6.25)	16.2 (5.85)
Baseline migraine hours			
Mean (SD)	170.8 (100.86)	171.2 (106.51)	177.4 (102.10)
Baseline headache hours			
Mean (SD)	201.4 (101.27)	199.5 (105.69)	210.3 (106.11)
Baseline percent of migraines with severe intensity			
Mean (SD)	46.78 (27.462)	48.69 (26.848)	49.21 (27.804)
Baseline average length in hours of migraine attack			
Mean (SD)	18.19 (17.695)	19.26 (25.392)	20.40 (23.013)

[*Note: copied from page 88 of the sponsor's study report*]

3.2.2.4 Efficacy Results and Conclusions

Based on the decision rules outlined in Section 3.2.2.2, the results for the primary endpoint and all of the key secondary endpoints for all dose groups were statistically significant.

Primary Efficacy Endpoint

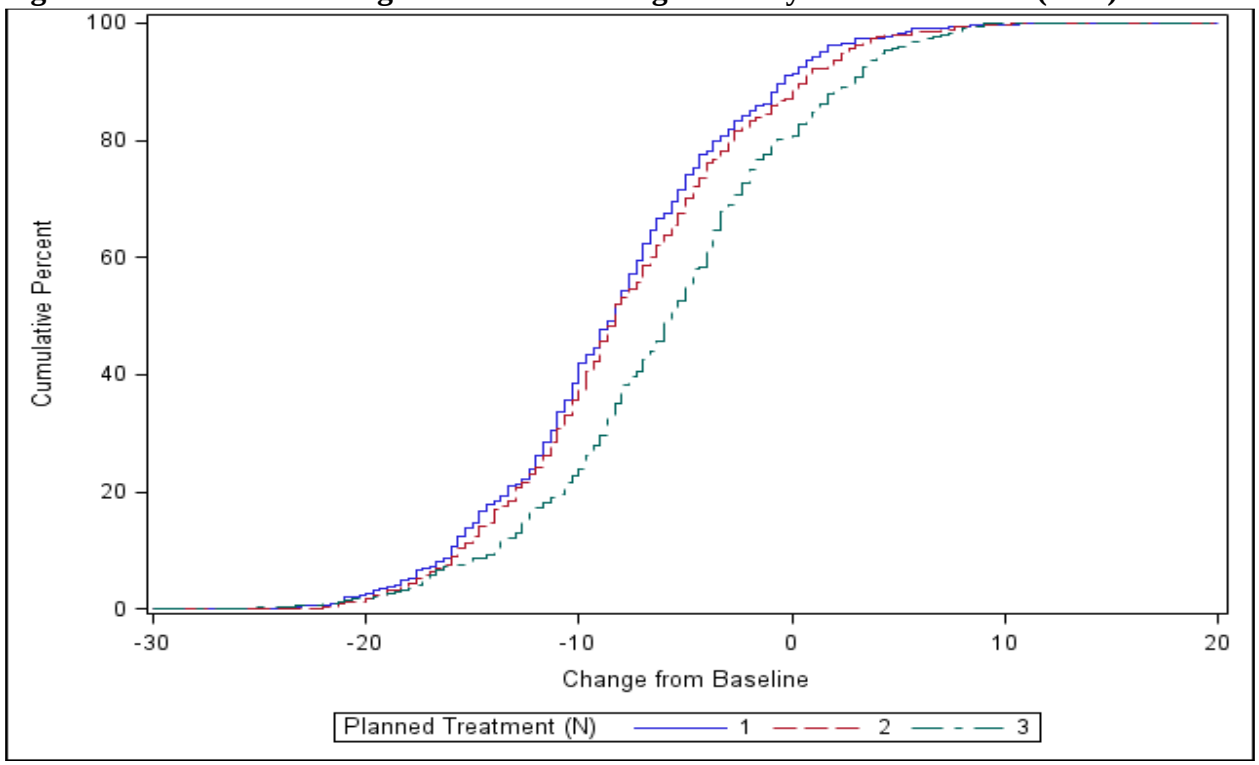
This primary efficacy endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of migraine days over Weeks 1-12.

Table 3-11 Analysis of Migraine Days by 12-Week Interval (FAS)

Parameters	ALD403 300 mg	ALD403 100 mg	Placebo
N	350	356	366
Mean Change from baseline	-8.2	-7.7	-5.6
Diff from Placebo Mean 95% CI p-value	 -2.59 (-3.45, -1.74) <0.0001	 -2.03 (-2.88, -1.17) <0.0001	
Decision	S	S	

With a mean difference of -2.59 days (95% CI: -3.45, -1.74), the ALD403 300 mg dose demonstrated a statistically significant improvement (P<0.0001) from placebo. The ALD403 100 mg dose also demonstrated a statistically significant improvement (P<0.0001) from placebo with a mean difference of -2.03 days (95% CI: -2.88, -1.18) for Weeks 1-12. Figure 3-6 presents the cumulative distribution function (CDF) of change from baseline migraine days for Weeks 1-12.

Figure 3-6 CDF of Change from Baseline Migraine Days for Weeks 1-12 (FAS)



Handling of Dropouts and Sensitivity Analysis

Nearly all subjects remained in the study through Week 12 with fewer than 13 subjects (<5%) in the 300-mg and 100-mg groups not attending the Week 12 visits and 10 placebo subjects not attending the Week 12 visit, see Table 3-12.

Table 3-12 Subjects Dropouts by through Week 12

Subjects by Visits	ALD403 300 mg	ALD403 100 mg	Placebo
Day 0	350	356	366
Week 12	344	349	356

Results of the sensitivity analyses based upon a modified missing data imputation rule (imputing baseline migraine days for subject who withdrew due to AEs, study burden or lack of efficacy) and modified definition of baseline (baseline is the 28 days prior to the first treatment instead of the first 28 days of screening) support the primary efficacy endpoint analysis. In these analyses, the upper limit of the confidence interval remains below zero demonstrating greater changes from baseline in the ALD403 groups compared with the placebo group. These results established the robustness and internal consistency of the treatment effects of the 300-mg and 100-mg dose groups compared to placebo.

Table 3-13 Sensitivity Analyses of Migraine Days by 12 Week Intervals

	ALD403 300 mg	ALD403 100 mg
[a]Mean Diff from Placebo (95% CI)	-2.5 (-3.38, -1.57)	-1.9 (-2.82, -1.01)
[b]Mean Diff from Placebo (95% CI)	-2.76 (-3.72, -1.80)	-2.11 (-3.06, -1.15)

[a] uses baseline results if a subject withdrew from the study due to an AE, study burden, lack of efficacy or death.
[b] uses the definition of baseline as the 28 days prior to treatment start date.

Key Secondary Efficacy Endpoints

Table 3-14 summarized the 75% migraine responder rate compared to placebo over Weeks 1-4 and Weeks 1-12, and 50% migraine responder rate compared to placebo for Weeks 1-12.

The 75% migraine responder rate over Weeks 1-4 demonstrated statistically significant improvements for the ALD403 300 mg and ALD403 100 mg group with estimated differences of 21.3% and 15.3% over placebo, respectively. The odds ratios of ALD403 300 mg and ALD403 100 mg over placebo were estimated as 3.21 and 2.45, respectively. Both groups passed statistical significances according to the multiplicity decision rule.

The 75% migraine responder rate over Weeks 1-12 demonstrated statistically significant improvements for ALD403 300 mg and 100 mg group with estimated differences of 18.1% and 11.7% over placebo group. The odds ratios of ALD403 300 mg and ALD403 100 mg over placebo were estimated as 2.78 and 2.05, respectively. Both groups passed statistical significances per the decision rule.

The 50% migraine responder rate over Weeks 1-12 demonstrated statistically significant improvements for ALD403 300 mg and 100 mg group with estimated differences of 22.1% and 18.2% over placebo group. The odds ratios of ALD403 300 mg and ALD403 100 mg over placebo were estimated as 2.45 and 2.10, respectively. Both groups passed statistical significances per the decision rule.

Table 3-14 Summary of Different Migraine Responder Rates (FAS)

Time Interval	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366
Weeks 1-4			
75% Responder (%)	129 (36.9)	110 (30.9)	57 (15.6)
Diff vs. Placebo (95% CI)	21.3 (15.0, 27.6)	15.3 (9.3, 21.4)	
OR vs. Placebo (95% CI)	3.21 (2.24, 4.58)	2.45 (1.71, 3.51)	
p-value[a]	<0.0001	<0.0001	
Decision	S	S	
Weeks 1-12			
75% Responder (%)	116 (33.1)	95 (26.7)	55 (15.0)
Diff vs. Placebo (95% CI)	18.1 (12.0, 24.3)	11.7 (5.8,17.5)	
OR vs. Placebo (95% CI)	2.78 (1.94, 3.99)	2.05 (1.42, 2.97)	
p-value[a]	<0.0001	0.0001	
Decision	S	S	
Weeks 1-12			
50% Responder (%)	215 (61.4)	205 (57.6)	144 (39.3)
Diff vs. Placebo (95% CI)	22.1 (14.9, 29.2)	18.2 (11.1, 25.4)	
OR vs. Placebo (95% CI)	2.45 (1.81, 3.30)	2.10 (1.56. 2.82)	
p-value[a]	<0.0001	<0.0001	
Decision	S	S	

*Abbreviations: NS = nominally significant; S = significant; * = not significant*
[a] p-values obtained from CMH test

The percentage of subjects with a migraine on the day after dosing (Day 1) decreased in the ALD403 300 mg and 100 mg groups, respectively. When compared with placebo, the percentage of subjects with a migraine on the day after dosing (Day 1) in the ALD403 300 mg and 100 mg groups were both significantly lower (per the decision rule) than the placebo group, see Table 3-15.

Table 3-15 Summary of Percentages of Subjects with a Migraine on the day after dosing

Assessment	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366
Percentage of subjects with a migraine			
Baseline[a]	57.4	57.5	58.0
Day 0[b]	33.1	40.0	45.3
Day 1	27.8	28.6	42.3
p-value[c]	< 0.0001	< 0.0001	

[c] p-values for the key secondary endpoint percentage of subjects with a migraine on the day after dosing (Day 1) were obtained from an CMH test.

Reduction in Migraine Prevalence from Baseline to Week 4

Table 21 presented the analysis of average daily migraine prevalence and reduction from baseline for Weeks 1-4. The mean difference of the change from baseline in average daily migraine prevalence over Weeks 1-4 was -11.0 (95% CI: -14.22, -7.77) for the ALD403 300 mg

arm, while the difference was -8.26 (95% CI: -11.48, -5.05) for the ALD403 100 mg arm, both statistically significant versus placebo (P<0.0001), per decision rule.

Table 3-16 Analysis of Reduction in Migraine Prevalence by Weeks 1-4

Interval	ALD403 300 mg N = 350	ALD403 100 mg N = 356	Placebo N = 366
Overall Weeks 1-4			
Actual			
Estimated mean	27.9	30.6	38.9
Mean difference from placebo	-11.00	-8.26	
95% CI	(-14.22, -7.77)	(-11.48, -5.05)	
Change from baseline[a]			
Estimated mean	-29.8	-27.1	-18.8
Mean difference from placebo	-11.00	-8.26	
95% CI	(-14.22, -7.77)	(-11.48, -5.05)	
p-value[b]	<0.0001	<0.0001	

Headache Impact Test and Acute Migraine Medication Usage

The statistical comparisons for the final two key secondary endpoints were only specified for the ALD403 300 mg group versus placebo. Table 3-17 presented a mean difference of -2.88 (95% CI: -3.91, -1.84) assessed at Week 12 in HIT-6 impact score, the ALD403 300 mg dose demonstrated a statistically significant improvement (P<0.0001) from placebo. Furthermore, the reductions in acute migraine medication days from baseline were numerically greater in the ALD403 groups with statistically significant reduction of -1.38 (95% CI: -1.88, -0.87) compared to placebo in the ALD403 300 mg group (P<0.0001).

Table 3-17 Summary and Analysis of HIT-6 and Acute Med Usage

Key Secondary Family #5	Visits	ALD403 300 mg N=350	Placebo N=366
HIT-6	Baseline	65.1	64.8
	Wks 9-12	57.6	60.5
	Change from baseline	-7.5	-4.3
	Diff from placebo (95% CI)	-2.88 (-3.91, -1.84)	
	p-value*	<0.0001	
Acute Medication Usage	Baseline	6.7	6.2
	Wks 1-12	3.2	4.3
	Change from baseline	-3.5	-1.9
	Diff from placebo (95% CI)	-1.38 (-1.88, -0.87)	
	p-value*	<0.0001	

* The p-values are from an ANCOVA model

Statistical Significance of Efficacy Endpoints
Based on the decision rule outlined in Figure 3-4, ALD403 300 mg and 100 mg groups both achieved the primary efficacy endpoint and all key secondary endpoints in the pre-specified statistical hierarchy.

3.3 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Race group

4.1.1 ALD403-CLIN-006 STUDY

Figure 4-1 presented a forest plot of difference from placebo in migraine days change from baseline over Weeks 1-12 by subgroup for ALD403 300 mg. The ALD403 300 mg group showed consistent reductions from baseline in monthly migraine days when compared with placebo across all clinically important subgroups.

Figure 4-1 Forest Plot of Difference from Placebo in Monthly Migraine Days Change from Baseline Over Weeks 1-12 by Subgroup - ALD403 300 mg

Variable	Subgroups	Change from Baseline ALD403 300 MG	Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-4.32	-3.07	-1.3	(-1.91, -0.59)
Age Group at Diagnosis	<=21 years	-4.59	-2.86	-1.7	(-2.66, -0.80)
	>21 years	-3.99	-3.29	-0.7	(-1.65, 0.25)
Age (years)	<=35	-4.13	-3.17	-1.0	(-2.06, 0.14)
	>35	-4.45	-3.01	-1.4	(-2.28, -0.61)
Sex	F	-4.33	-3.01	-1.3	(-2.04, -0.61)
	M	-4.21	-3.39	-0.8	(-2.70, 1.05)
Race	White	-4.43	-2.99	-1.4	(-2.20, -0.69)
	Black	-3.77	-3.58	-0.2	(-1.81, 1.42)
	Other	-3.53	-3.00	-0.5	(-3.09, 2.02)
Ethnic	Not Hispanic	-4.25	-2.90	-1.4	(-2.09, -0.61)
	Hispanic	-4.66	-4.02	-0.6	(-2.15, 0.87)

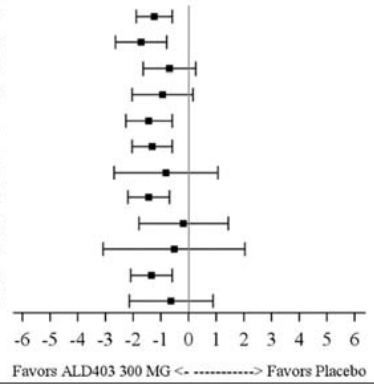
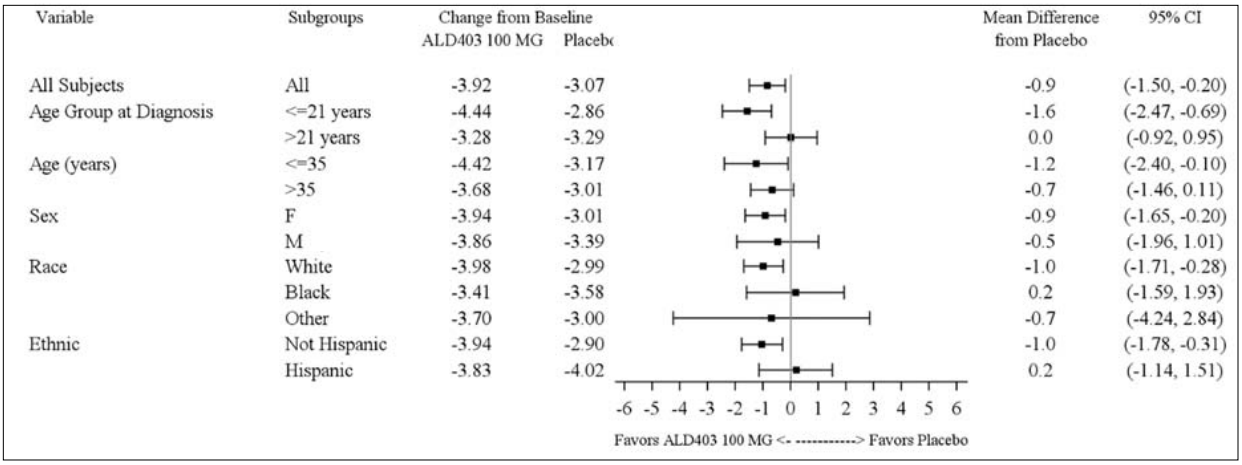


Figure 4-2 is the similar forest plot for ALD403 100 mg versus placebo. Overall, the reductions from baseline in the ALD403 300-mg group were more robust and consistent across the analyzed subgroups compared to ALD403 100-mg group.

Figure 4-2 Forest Plot of Difference from Placebo in Monthly Migraine Days Change from Baseline Over Weeks 1-12 by Subgroup - ALD403 100 mg



4.1.2 ALD403-CLIN-011 STUDY

Figure 4-3 presented a forest plot of difference from placebo in migraine days change from baseline over Weeks 1-12 by subgroup for ALD403 300 mg. The ALD403 300 mg group showed consistent reductions from baseline in monthly migraine days when compared with placebo across all clinically important subgroups.

Figure 4-3 Forest Plot of Difference from Placebo in Migraine Days Change from Baseline Over Weeks 1-12 by Subgroup - ALD403 300 mg

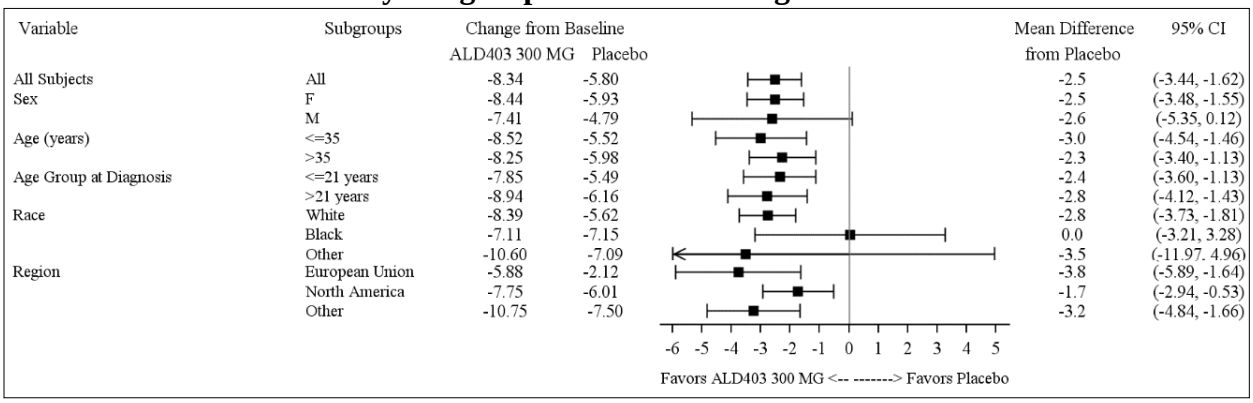
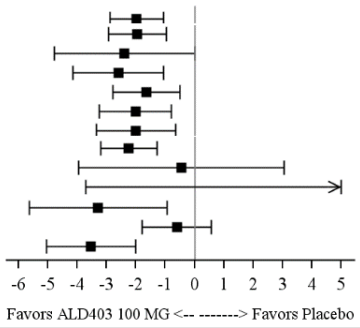


Figure 4-4 is the similar forest plot for ALD403 100 mg versus placebo. Overall, the reductions from baseline in the ALD403 300-mg group were more robust and consistent across the analyzed subgroups compared to ALD403 100-mg group.

Figure 4-4 Forest Plot of Difference from Placebo in Migraine Days Change from Baseline Over Weeks 1-12 by Subgroup - ALD403 100 mg

Variable	Subgroups	Change from Baseline ALD403 100 MG	Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-7.78	-5.80	-2.0	(-2.89, -1.07)
Sex	F	-7.88	-5.93	-1.9	(-2.93, -0.96)
	M	-7.18	-4.79	-2.4	(-4.79, 0.01)
Age (years)	<=35	-8.12	-5.52	-2.6	(-4.14, -1.06)
	>35	-7.63	-5.98	-1.6	(-2.78, -0.51)
Age Group at Diagnosis	<=21 years	-7.51	-5.49	-2.0	(-3.26, -0.78)
	>21 years	-8.16	-6.16	-2.0	(-3.35, -0.64)
Race	White	-7.86	-5.62	-2.2	(-3.20, -1.29)
	Black	-7.60	-7.15	-0.5	(-3.96, 3.05)
	Other	-0.11	-7.09	7.0	(-3.70, 17.67)
Region	European Union	-5.41	-2.12	-3.3	(-5.64, -0.93)
	North America	-6.61	-6.01	-0.6	(-1.79, 0.58)
	Other	-11.03	-7.50	-3.5	(-5.05, -2.02)



4.2 Other Subgroup Populations

4.2.1 ALD403-CLIN-006 STUDY

This section explored subgroup analyses by patient's baseline migraine days (<=9 or > 9 days) and migraine history (<=15 or > 15 years). Again, these subgroups also numerically favoring the ALD403 300 and 100 mg over placebo, see Figure 4-5 and Figure 4-6.

Figure 4-5 Subgroup by Migraine history- ALD403 300 mg vs. Placebo

Variable	Subgroups	Change from Baseline ALD403 300 MG	Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-4.32	-3.07	-1.3	(-1.91, -0.59)
Baseline Migraine Days	<=9	-3.61	-2.13	-1.5	(-2.22, -0.73)
	>9	-5.58	-4.80	-0.8	(-1.94, 0.37)
Duration of Migraines (years)	<=15 years	-4.20	-3.20	-1.0	(-2.03, 0.03)
	>15 years	-4.41	-2.93	-1.5	(-2.36, -0.62)

Figure 4-6 Subgroup by Migraine history- ALD403 100 mg vs. Placebo

Variable	Subgroups	Change from Baseline ALD403 100 MG	Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-3.92	-3.07	-0.9	(-1.50, -0.20)
Baseline Migraine Days	<=9	-3.25	-2.13	-1.1	(-1.85, -0.38)
	>9	-5.14	-4.80	-0.3	(-1.45, 0.78)
Duration of Migraines (years)	<=15 years	-3.60	-3.20	-0.4	(-1.40, 0.61)
	>15 years	-4.22	-2.93	-1.3	(-2.12, -0.47)

4.2.2 ALD403-CLIN-011 STUDY

This section explored subgroup analyses by patient's baseline migraine days (<=17 or > 17 days) and migraine history (<=15 or > 15 years). Again, these subgroups also numerically favoring the ALD403 300 and 100 mg over placebo, see Figure 4-7 and Figure 4-8.

Figure 4-7 Subgroup by Migraine history- ALD403 300 mg

Variable	Subgroups	Change from Baseline ALD403 300 MG	Change from Baseline Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-8.34	-5.80	-2.5	(-3.44, -1.62)
Baseline Migraine Days	<17 days	-7.38	-4.28	-3.1	(-4.12, -2.08)
	>=17 days	-9.52	-7.73	-1.8	(-3.32, -0.25)
Duration of Migraines (years)	<=15 years	-8.27	-5.96	-2.3	(-3.65, -0.97)
	>15 years	-8.39	-5.64	-2.8	(-4.00, -1.50)

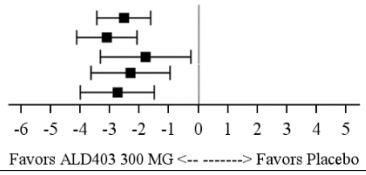
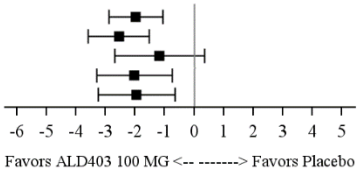


Figure 4-8 Subgroup by Migraine history- ALD403 100 mg

Variable	Subgroups	Change from Baseline ALD403 100 MG	Change from Baseline Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-7.78	-5.80	-2.0	(-2.89, -1.07)
Baseline Migraine Days	<17 days	-6.83	-4.28	-2.6	(-3.58, -1.53)
	>=17 days	-8.90	-7.73	-1.2	(-2.70, 0.35)
Duration of Migraines (years)	<=15 years	-7.99	-5.96	-2.0	(-3.31, -0.74)
	>15 years	-7.58	-5.64	-1.9	(-3.25, -0.65)



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

It is notable that to address multiplicity, a serial, fixed-sequence procedure was used to consecutively and conservatively test hierarchically-ordered hypotheses at level α until the first non-rejection in both pivotal studies. Many other less conservative multiplicity procedures will also conclude the statistically significant finding in the primary endpoint for 30-mg group in Study 006.

Collective evidence is not formally considered in this review since there was one double-blind, controlled trial in Chronic Migraine and one in Episodic Migraine which are considered distinct populations.

5.2 Conclusions and Recommendations

Overall, results from the 2 pivotal studies demonstrated that ALD403 is an effective migraine preventive treatment in adults with either EM or CM. ALD403 administered by IV infusion results in a rapid and robust therapeutic effect for migraine prevention that is observed on the day after the initial dose.
In summary:

- ALD403 administered every 3 months by IV infusion results in a statistically significant reduction in monthly migraine days, as demonstrated by the results on the primary efficacy analysis - the change from baseline in mean monthly migraine days over the week 1-12 interval (the dosing cycle length).
- The therapeutic benefit resulting from administration of ALD403 for the preventive treatment of migraine in adults is robust and clinically meaningful, as demonstrated by the results of the 75% and 50% migraine responder analyses.
- Following ALD403 administration, a robust migraine preventive effect is rapidly established from day 1 and consistently maintained over the 3-month dosing cycle. Following a second

infusion, the magnitude of the migraine preventive effect is consistently maintained through the second dosing cycle.

- ALD403 treatment results in reduced use of acute migraine medications.
- ALD403 treatment reduces the impact that migraine imposes on individuals as demonstrated by results of the HIT-6.

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/s/

STEVE G BAI
11/04/2019 07:37:28 PM

KUN JIN
11/07/2019 09:28:46 AM
I concur with the review.

HSIEN MING J HUNG
11/07/2019 09:53:27 AM