NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Erenumab

Trial Indication(s)

Migraine

Protocol Number

CAMG334ADE01

Protocol Title

Head-to-head study of Erenumab against topiRamate-a double-blind, double dummy Migraine study to assess tolerability and efficacy in a patiEnt –centered Setting

Clinical Trial Phase

Phase 4

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: February 2019 (Actual)
Primary Completion Date: July 2020 (Actual)
Study Completion Date: July 2020 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This study used a single-cohort, 2-treatment arm, parallel-group randomized, double-blind, double-dummy design in adult patients with episodic migraine and chronic migraine1, who had to be either naïve or not suitable for or could have failed up to three prophylactic treatments out of: propranolol/metoprolol, amitriptyline, flunarizine. Patients were stratified into groups according to their number of migraine days during the baseline epoch.

Centers

Germany(82)

Objectives:

Primary objective was to demonstrate the tolerability of 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose assessed by the rate of patients discontinuing treatment due to AE during the double-blind epoch of the study.

Secondary objective was to evaluate the effect of erenumab compared to topiramate in the highest tolerated dose on the proportion of patients with at least 50% reduction from baseline in monthly migraine days.

Exploratory objectives were:

- To evaluate the effect of 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose on functional impairment, as measured by the HIT-6
- To evaluate the effect of 70 mg and 140 mg erenumab compared to topiramate in the highest tolerated dose on generic health-related quality of life, as measured by the SF-36 v.2

[1] According to amendment 02, 06 June 2019

Test Product (s), Dose(s), and Mode(s) of Administration

The IMP was supplied in a double-dummy setting.

70 mg and 140 mg erenumab (or respective placebos) were administered subcutaneously by qualified study staff at each dosing visit during the 24 week DBTE (i.e., at Day 1 and Week 4, Week 8, Week 12, Week 16 and Week 20) in the upper arm, upper thigh, or abdomen.

Topiramate and oral placebo were administered by the patient himself. During the first week of the titration phase topiramate 25 mg or matching placebo were administered once daily. After the first week, topiramate titration was done according to the SmPC in 25 mg increments each week and aimed to reach the recommended daily treatment dose of 100 mg (50/75/100 mg). Topiramate 50/75/100 mg or matching placebo were administered twice daily during titration phase and maintenance phase. Control-IMP should be tapered off by patients who completed the study or discontinued study treatment after receiving a daily dose of 75 mg or 100 mg control-IMP by reducing the daily dose of control-IMP by 50 mg for one week.

Statistical Methods

The primary endpoint of the study was discontinuation of treatment due to AE during the double-blind epoch of the study.

- The analysis on primary endpoint was done based on the intended population of the FAS.
- Variable of interest – the primary endpoint was the rate of patients discontinuing the allocated study treatment due to an AE during the DBTE.
- Intervention effect – effect between erenumab versus topiramate during double-blind treatment regardless of adherence to randomized treatment.
- Summary measure – odds ratio

The secondary endpoint was the achievement of at least a 50% reduction from baseline in MMDs over the last 3 months (months 4, 5, and 6) of the DBTE.

The analysis of the secondary variable was done based on the following estimand:

- Population – Full Analysis Set (FAS)
- Variable of Interest – number of patients with at least 50% reduction from baseline in monthly migraine days (MMD)
- Intercurrent event: discontinuation of study medication – effect between erenumab versus topiramate assuming to evaluate treatment policy

- Intercurrent event: discontinuation of study or lost to follow up – effect between erenumab versus topiramate assuming no response could be achieved
- Summary measure – odds ratio

All the patients' data collected regarding 50% response of MMD were used in the analysis regardless whether patients completed the study drug or not.

Exploratory efficacy analyses of erenumab in comparison to topiramate was based on patients' reported data assessed via eDiary, including

- Patients' quality of life assessed with SF-36v2 (The Short Form (36) Health Survey)
- Headache impact on patients' functional ability assessed by HIT-6 (Headache Impact Test)

Methods of analysis for exploratory efficacy analyses are summarized in the table below.

Exploratory Endpoint	Model	Terms included in the model	Imputation of missing values	Additional
Proportion of patients achieving at least a 5 points reduction from baseline in HIT-6 total score	Logistic regression model	- treatment group - baseline value - stratification factor	Non-response imputation	Summary statistics for observed data Relative Risk** Risk Difference**
SF-36 quality of life: Proportion of patients achieving at least 5 points increase from baseline to week 24 in PCS and MCS	Logistic regression model	- treatment group - baseline value - stratification factor	Non-response imputation	Summary statistics for observed data Relative Risk** Risk Difference**

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
1) Documented history of migraine in the 12 months prior to screen
2) at least 4 days per month of migraine symptoms
3) >=80% diary compliance during the Baseline period
4) Patients must be either naïve or not suitable or have failed previous migraine prophylactic treatments

Key Exclusion Criteria:
1) Older than 50 years of age at migraine onset

2) Pregnant or nursing
3) History of cluster or hemiplegic headache
4) History or evidence of major psychiatric disorder
5) Score of 19 or higher on Beck Depression Inventory (BDI)

Participant Flow Table

Overall Study

	Erenumab	Topiramate	Total
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)	
Started	389	388	777
Full Analysis set (FAS)	388	388	776
Safety Analysis Set (SAF)	388	388	776
Completed	373	366	739
Not Completed	16	22	38
Adverse Event	3	12	15
Patient's/guardian's decision	3	5	8
Lost to Follow-up	4	2	6
Protocol Violation	3	2	5
Withdrawal of informed consent	2	1	3
New therapy for study indication	1	0	1

Baseline Characteristics

	Erenumab	Topiramate	Total
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)	
Number of Participants [units: participants]	388	388	776
Age Continuous (units: Years) Mean ± Standard Deviation			
	40.8±12.4	40.7±12.4	40.7±12.4
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	331	335	666
Male	57	53	110
Race/Ethnicity, Customized (units: Participants)			
Caucasian	383	387	770
Asian	1	0	1
Unknown	1	0	1
Other	3	1	4
Baseline Monthly Migraine Days (MMDs) categories[1] (units: Participants) Count of Participants (Not Applicable)			
< 4 days	2	0	2
4 to 7 days	94	92	186
8 to 14 days	248	254	502
>= 15 days	43	42	85

Missing	1	0	1

[1] Monthly migraine days at baseline are the number of migraine days in the baseline period that are normalized in a 28-day interval. Monthly migraine days after baseline are the number of migraine days between each monthly IMP dose that are normalized in a 28-day interval. Days without eDiary data in each normalized monthly interval were prorated.

Primary Outcome Result(s)

Proportion of patients with treatment discontinuation due to an Adverse Event (AE) during the double-blind treatment epoch/period (DBTE)

(Time Frame: 24 Weeks)

	Erenumab	Topiramate
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Number of Participants Analyzed [units: participants]	388	388
Proportion of patients with treatment discontinuation due to an Adverse Event (AE) during the double-blind treatment epoch/period (DBTE) (units: Participants) Count of Participants (Not Applicable)		
	41 (10.57%)	151 (38.92%)

Statistical Analysis

Groups	Erenumab, Topiramate	
P Value	<.001	
Method	Regression, Logistic	Odds ratio is obtained from a logistic regression model that includes treatment group and stratification factor (MMD at baseline)

Odds Ratio (OR)	0.19
95 % Confidence Interval 2-Sided	0.13 to 0.27

Secondary Outcome Result(s)

Number of patients with at least 50% reduction from baseline in monthly migraine days (MMD) over the last three months (month 4, 5, and 6)

(Time Frame: Baseline, Last three months (month 4, 5, and 6))

	Erenumab	Topiramate
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Number of Participants Analyzed [units: participants]	388	388
Number of patients with at least 50% reduction from baseline in monthly migraine days (MMD) over the last three months (month 4, 5, and 6) (units: Participants) Count of Participants (Not Applicable)		
	215 (55.41%)	121 (31.19%)

Statistical Analysis

Groups	Erenumab, Topiramate	
P Value	<.001	
Method	Regression, Logistic	Odds ratio is obtained from a logistic regression model that includes treatment group and stratification factor (MMD at baseline)
Odds Ratio (OR)	2.76	

95 % Confidence Interval 2-Sided	2.06 to 3.71

Other Pre-Specifed Outcome Result(s)

EXPLORATORY ENDPOINT: Proportion of patients achieving at least a 5 points reduction in the Headache Impact Test (HIT-6) from baseline to week 24

(Time Frame: Baseline, Week 24)

	Erenumab	Topiramate
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Number of Participants Analyzed [units: participants]	388	388
EXPLORATORY ENDPOINT: Proportion of patients achieving at least a 5 points reduction in the Headache Impact Test (HIT-6) from baseline to week 24 (units: Participants) Count of Participants (Not Applicable)		
	280 (72.16%)	209 (53.87%)

Statistical Analysis

Groups	Erenumab, Topiramate	
P Value	<.001	
Method	Regression, Logistic	Odds ratio is obtained from a logistic regression model that includes treatment group and stratification factor (MMD at baseline)
Odds Ratio (OR)	2.30	
95 % Confidence Interval 2-Sided	1.70 to 3.12	

EXPLORATORY ENDPOINT: Proportion of patients achieving at least a 5 points increase in the Medical Outcome Short Form Health Survey Version 2 (SF-36) from baseline to week 24

(Time Frame: Baseline, Week 24)

	Erenumab	Topiramate
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Number of Participants Analyzed [units: participants]	388	388
EXPLORATORY ENDPOINT: Proportion of patients achieving at least a 5 points increase in the Medical Outcome Short Form Health Survey Version 2 (SF-36) from baseline to week 24 (units: Participants) Count of Participants (Not Applicable)		
Physical Component Summary (PCS)	185 (47.68%)	145 (37.37%)
Mental Component Summary (MCS)	98 (25.26%)	65 (16.75%)

Statistical Analysis

Groups	Erenumab, Topiramate	Physical Component Summary (PCS)
P Value	<0.001	
Method	Regression, Logistic	Odds ratio is obtained from a logistic regression model that includes treatment group and stratification factor (MMD at baseline)
Odds Ratio (OR)	1.75	
95 % Confidence Interval 2-Sided	1.26 to 2.43	

Statistical Analysis

Groups	Erenumab, Topiramate	Mental Component Summary (MCS)

P Value	0.005	
Method	Regression, Logistic	Odds ratio is obtained from a logistic regression model that includes treatment group and stratification factor (MMD at baseline)
Odds Ratio (OR)	1.79	
95 % Confidence Interval 2-Sided	1.29 to 2.69	

Safety Results

All-Cause Mortality

	Erenumab N = 388	Topiramate N = 388
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until 8 weeks after the last Investigational Medicinal product (IMP) injection, assessed up to approximately 33 weeks (treatment duration ranged from 4.0 to 25.1 weeks).
Additional Description	Any sign or symptom that occurs during the study treatment until 8 weeks after the last Investigational Medicinal product (IMP) injection. Maximum exposure to study treatments = 25 weeks (Erenumab treatment group) and 25.1 weeks (Topiramate treatment group).
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment

	Erenumab N = 388	Topiramate N = 388
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Total participants affected	10 (2.58%)	19 (4.90%)
Eye disorders		
Angle closure glaucoma	0 (0.00%)	1 (0.26%)
Retinal detachment	0 (0.00%)	1 (0.26%)

Rhegmatogenous retinal detachment	0 (0.00%)	1 (0.26%)
Gastrointestinal disorders		
Gastritis	0 (0.00%)	1 (0.26%)
Irritable bowel syndrome	0 (0.00%)	1 (0.26%)
Mechanical ileus	1 (0.26%)	0 (0.00%)
Obstructive defaecation	1 (0.26%)	0 (0.00%)
Hepatobiliary disorders		
Cholelithiasis	0 (0.00%)	1 (0.26%)
Immune system disorders		
Anaphylactic shock	0 (0.00%)	1 (0.26%)
Infections and infestations		
Appendicitis	0 (0.00%)	1 (0.26%)
Bacteriuria	0 (0.00%)	1 (0.26%)
Gastroenteritis	0 (0.00%)	1 (0.26%)
Gastrointestinal infection	0 (0.00%)	1 (0.26%)
Influenza	0 (0.00%)	1 (0.26%)
Nasopharyngitis	0 (0.00%)	1 (0.26%)
Papilloma viral infection	1 (0.26%)	0 (0.00%)
Parasitic gastroenteritis	0 (0.00%)	1 (0.26%)
Pyelonephritis	0 (0.00%)	1 (0.26%)
Injury, poisoning and procedural complications		
Ankle fracture	0 (0.00%)	1 (0.26%)

Concussion	0 (0.00%)	1 (0.26%)
Contusion	1 (0.26%)	0 (0.00%)
Fall	1 (0.26%)	0 (0.00%)
Ligament rupture	1 (0.26%)	0 (0.00%)
Limb injury	1 (0.26%)	0 (0.00%)
Skin laceration	1 (0.26%)	0 (0.00%)
Sternal fracture	1 (0.26%)	0 (0.00%)
Tendon injury	1 (0.26%)	0 (0.00%)
Investigations		
Weight decreased	0 (0.00%)	1 (0.26%)
Metabolism and nutrition disorders		
Decreased appetite	0 (0.00%)	1 (0.26%)
Musculoskeletal and connective tissue disorders		
Intervertebral disc protrusion	1 (0.26%)	0 (0.00%)
Lumbar spinal stenosis	0 (0.00%)	1 (0.26%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Fibroadenoma of breast	0 (0.00%)	1 (0.26%)
Nervous system disorders		
Migraine	0 (0.00%)	1 (0.26%)
Migraine with aura	1 (0.26%)	0 (0.00%)
Syncope	0 (0.00%)	1 (0.26%)

Psychiatric disorders		
Depression	0 (0.00%)	1 (0.26%)
Major depression	1 (0.26%)	0 (0.00%)
Reproductive system and breast disorders		
Cervical dysplasia	1 (0.26%)	0 (0.00%)
Dysmenorrhoea	1 (0.26%)	0 (0.00%)
Endometriosis	0 (0.00%)	1 (0.26%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until 8 weeks after the last Investigational Medicinal product (IMP) injection, assessed up to approximately 33 weeks (treatment duration ranged from 4.0 to 25.1 weeks).
Additional Description	Any sign or symptom that occurs during the study treatment until 8 weeks after the last Investigational Medicinal product (IMP) injection. Maximum exposure to study treatments = 25 weeks (Erenumab treatment group) and 25.1 weeks (Topiramate treatment group).
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Erenumab N = 388	**Topiramate N = 388**
Arm/Group Description	70 mg and 140 mg Erenumab	Topiramate in the highest tolerated dose (50 - 100 mg/day)
Total participants affected	253 (65.21%)	331 (85.31%)
Ear and labyrinth disorders		

Vertigo	20 (5.15%)	24 (6.19%)
Gastrointestinal disorders		
Abdominal pain upper	22 (5.67%)	23 (5.93%)
Constipation	48 (12.37%)	12 (3.09%)
Diarrhoea	20 (5.15%)	29 (7.47%)
Nausea	36 (9.28%)	71 (18.30%)
General disorders and administration site conditions		
Fatigue	44 (11.34%)	74 (19.07%)
Infections and infestations		
Nasopharyngitis	145 (37.37%)	150 (38.66%)
Investigations		
Weight decreased	5 (1.29%)	22 (5.67%)
Metabolism and nutrition disorders		
Decreased appetite	8 (2.06%)	39 (10.05%)
Musculoskeletal and connective tissue disorders		
Back pain	21 (5.41%)	20 (5.15%)
Nervous system disorders		
Disturbance in attention	18 (4.64%)	63 (16.24%)
Dizziness	28 (7.22%)	60 (15.46%)
Dysgeusia	3 (0.77%)	23 (5.93%)

Paraesthesia	17 (4.38%)	159 (40.98%)
Taste disorder	0 (0.00%)	26 (6.70%)
Psychiatric disorders		
Sleep disorder	20 (5.15%)	8 (2.06%)

Other Relevant Findings

None

Conclusion:

The HER-MES study distinctly showed that treatment with erenumab has a significantly better tolerability profile and a superior efficacy compared to topiramate. The primary endpoint clearly demonstrated that erenumab was better tolerated than topiramate, leading to much less treatment discontinuations due to AEs in this study group. The statistical significant difference in the 50% responder rate in favor for erenumab was supported by the good results of the other efficacy analyses including PROs such as functional impairment and quality of life, which all resulted in clinically meaningful and statistically significant superiority of erenumab over topiramate on a nominal level (p-values not adjusted for multiple testing).

The safety results for erenumab were in accordance with the overall safety and tolerability profile observed across the phase 2 and 3 study program. The slightly higher discontinuation rate due to AE compared to the placebo-controlled phase 2 and 3 studies can be largely attributed to a nocebo effect introduced by the rigorous double-dummy design. No clinical significant dose related tolerability concerns arose during this study. No new or unexpected finding were observed.

The HER-MES study supports the potential of erenumab in overcoming issues of low adherence in clinical practice observed with oral preventive drugs, lessening migraine burden and improving quality of life in a broad migraine population.

Data from this study will provide important data for clinicians treating migraine patients as particularly in comparison to current treatment options. In addition, this data will also be used to support national health technology assessments (HTAs) and reimbursement negotiations.

The risk of bias for the primary endpoint due to implications of the COVID-19 pandemic could be excluded. A possible influence on some secondary/exploratory endpoints would affect both treatment groups to the same degree and should not bias a comparison of treatment groups.

Therefore, the overall impact of the COVID-19 pandemic on this study can be neglected.

Date of Clinical Trial Report

17-May-2021