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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Erenumab

Trial Indication(s)

Episodic migraine (EM), chronic migraine (CM)

Protocol Number

CAMG334ADE03

Protocol Title

Assessment of Prolonged safety and tOLerability of erenumab in migraine patients in a Long-term OpeN-label study (APOLLON)

Clinical Trial Phase

Phase 4

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: September 30, 2019 (Actual)

Primary Completion Date: February 23, 2023 (Actual)

Study Completion Date: March 13, 2023 (Actual)

Study Design/Methodology

This was an open-label, multi-center, single arm study with flexible dosing allowing both dose adjustment and one drug holiday per patient.

The study design consisted of 3 parts:

- Screening Epoch (0 - 2 weeks): required for all patients to assess initial eligibility. Eligible patients came from study CAMG334ADE01 (NCT03828539).
- Open-label Treatment Epoch (128 weeks): Individual patients were treated for 128 weeks. In this open-label treatment phase, the erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit. Additionally, a voluntary single treatment interruption ('drug holiday') of up to 24 weeks (approximately six months) could be introduced after at least 12 weeks of treatment in the open-label Treatment Epoch.
- Follow-up Epoch (4 weeks): A Follow-Up Visit 4 weeks after the last regular study visit (8 weeks after last investigational medicinal product [IMP] application) was required as part of routine safety monitoring.

Centers

Germany(79)

Objectives:

Both primary and secondary objectives were to evaluate the long-term safety of 70 and 140 mg erenumab in patients with EM or CM.

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

The study treatment was erenumab. Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit. Erenumab was supplied in pre-filled autoinjectors containing 70 mg or 140 mg erenumab. Study treatment was administered by subcutaneous injection every 4 weeks.

The planned duration of treatment was 128 weeks for individual patients. However, each patient was eligible to one voluntary treatment interruption of up to 24 weeks (approximately 6 months) after an initial treatment duration of at least 12 weeks. After such a voluntary treatment interruption within the 128 weeks of the Treatment Epoch patients could return to the treatment schedule.

Subjects could be discontinued from treatment earlier due to unacceptable adverse events and/or at the discretion of the investigator or the subject.

Statistical Methods

The Safety Set (SAF) comprised all patients who received at least one dose of study treatment in the Open-label Treatment Epoch of this study.

The primary analysis (exposure adjusted incidence rate of AEs, EAIR) was conducted dividing the number of AEs by the time under treatment and standardizing it per 100 patient-years. Exact Pearson-Clopper confidence intervals for single proportions were calculated to evaluate the precision of the estimated parameter. No formal hypotheses testing was conducted.

Primary endpoint was the EAIR of AE during open-label Treatment Epoch per 100 subject years.

Secondary endpoints were the proportion of patients discontinuing open-label Treatment Epoch due to AE or non-AE reasons.

Study Population: Key Inclusion/Exclusion Criteria

The study population consisted of patients with a documented history of episodic (4 – 14 baseline migraine days) or chronic migraine (≥15 baseline headache days), who had been successfully randomized to clinical trial CAMG334ADE01.

Key inclusion Criteria:

– Signed informed consent must be obtained prior to participation in the study

- Patient is capable of understanding the nature, significance and implications of the clinical trial
- Adults ≥18 years of age upon entry into screening

Key exclusion Criteria:

- Use of a prophylactic migraine medication within five plasma clearance half-lives, or a device or procedure within one month prior to the start of the Open-label Treatment Epoch. This exclusion criteria does not apply to erenumab or topiramate administered within clinical trial CAMG334ADE01
- Any prior exposure to (investigational) prophylactic migraine products targeting the CGRP pathway, other than erenumab

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Participant Flow Table

Overall Study

	Erenumab	Total
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.	
Started	701	701
Completed	534	534
Not Completed	167	167
Subject/guardian decision	91	91
Adverse Event	24	24
Lost to Follow-up	19	19
New therapy for study indication	9	9
Pregnancy	9	9
Withdrawal of informed consent	8	8
Physician Decision	4	4
Protocol Deviation	3	3

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Baseline Characteristics

	Erenumab	Total
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.	
Number of Participants [units: participants]	701	701
Baseline Analysis Population Description		
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation		
	41.8±12.3	
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Female	608	608
Male	93	93
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
White	695	695
Asian	1	1
Unknown	1	1
Other	4	4

Primary Outcome Result(s)

Exposure adjusted incidence rate of AE during Open-label Treatment Epoch per 100 subject years

Description	This outcome measure was calculated dividing the number of adverse events (AEs) by the total patient exposure time and standardizing it per 100 patient-years. Exact Pearson-Clopper confidence intervals for single proportions were calculated to evaluate the precision of the estimated parameter.
Time Frame	Up to 128 weeks
Analysis Population Description	Safety set (SAF) defined as all patients who received at least one dose of study treatment in the Open-label Treatment Epoch of this study.

	Erenumab
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.
Number of Participants Analyzed [units: participants]	701
Exposure adjusted incidence rate of AE during Open-label Treatment Epoch per 100 subject years (units: number of AEs per 100 patient-years)	**Number (95% Confidence Interval)**
	101.71 (92.28 to 111.14)

Secondary Outcome Result(s)

Proportion of patients discontinuing Open-label Treatment Epoch due to AE

Description	Participants discontinuing the Open-label Treatment Epoch due to adverse events (AEs) to evaluate the long-term tolerability of erenumab in patients with episodic migraine or chronic migraine.

Time Frame	Up to 128 weeks
Analysis Population Description	Safety set (SAF) defined as all patients who received at least one dose of study treatment in the Open-label Treatment Epoch of this study.

	Erenumab
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.
Number of Participants Analyzed [units: participants]	701
Proportion of patients discontinuing Open-label Treatment Epoch due to AE (units: Participants)	**Count of Participants (Percentage)**
	29 (4.14%)

Proportion of patients discontinuing Open-label Treatment Epoch due to non-AE reasons

Description	Participants discontinuing the Open-label Treatment Epoch due to non-AE reasons to evaluate the long-term tolerability of erenumab in patients with episodic migraine or chronic migraine.
Time Frame	Up to 128 weeks
Analysis Population Description	Safety set (SAF) defined as all patients who received at least one dose of study treatment in the Open-label Treatment Epoch of this study.

	Erenumab
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.
Number of Participants Analyzed [units: participants]	701

Proportion of patients discontinuing Open-label Treatment Epoch due to non-AE reasons (units: Participants)	**Count of Participants (Percentage)**
	126 (17.97%)

Safety Results

Time Frame	From first dose of study treatment in the Open-label Treatment Epoch of this study to 8 weeks after last dose (up to 132 weeks).
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Erenumab N = 701
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.
Total Number Affected	0
Total Number At Risk	701

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Serious Adverse Events

Time Frame	From first dose of study treatment in the Open-label Treatment Epoch of this study to 8 weeks after last dose (up to 132 weeks).
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

	Erenumab N = 701
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.
Total # Affected by any Serious Adverse Event	86
Total # at Risk by any Serious Adverse Event	701
Cardiac disorders	
Atrial fibrillation	1 (0.14%)
Myocardial infarction	1 (0.14%)
Tachycardia	2 (0.29%)
Congenital, familial and genetic disorders	
Macrocornea	1 (0.14%)
Ear and labyrinth disorders	
Vertigo	2 (0.29%)
Vestibular paroxysmia	1 (0.14%)

Endocrine disorders	
Goitre	1 (0.14%)
Eye disorders	
Cataract	1 (0.14%)
Lens dislocation	1 (0.14%)
Gastrointestinal disorders	
Abdominal pain lower	1 (0.14%)
Anal fistula	1 (0.14%)
Enteritis	1 (0.14%)
Eosinophilic oesophagitis	1 (0.14%)
Ileus	1 (0.14%)
Internal hernia	1 (0.14%)
Intestinal stenosis	1 (0.14%)
Large intestinal stenosis	1 (0.14%)
Large intestine polyp	1 (0.14%)
Volvulus	1 (0.14%)
General disorders and administration site conditions	
Asthenia	1 (0.14%)
Capsular contracture associated with breast implant	1 (0.14%)
Pain	1 (0.14%)
Pyrexia	1 (0.14%)
Hepatobiliary disorders	
Cholecystitis	1 (0.14%)

Cholelithiasis	2 (0.29%)
Immune system disorders	
Hypersensitivity	1 (0.14%)
Infections and infestations	
Appendicitis	4 (0.57%)
Appendicitis perforated	1 (0.14%)
Bartholinitis	1 (0.14%)
COVID-19	1 (0.14%)
Gastroenteritis	1 (0.14%)
Gastrointestinal viral infection	1 (0.14%)
Herpes zoster	1 (0.14%)
Infection	1 (0.14%)
Nephritis bacterial	1 (0.14%)
Pneumonia viral	1 (0.14%)
Root canal infection	1 (0.14%)
Tonsillitis	1 (0.14%)
Urinary tract infection	1 (0.14%)
Vestibular neuronitis	1 (0.14%)
Injury, poisoning and procedural complications	
Arthropod sting	2 (0.29%)
Bursa injury	1 (0.14%)
Contusion	1 (0.14%)
Epicondylitis	1 (0.14%)
Humerus fracture	1 (0.14%)

Ligament rupture	1 (0.14%)
Muscle rupture	1 (0.14%)
Post procedural haematoma	1 (0.14%)
Post-traumatic neck syndrome	1 (0.14%)
Road traffic accident	1 (0.14%)
Shoulder fracture	1 (0.14%)
Musculoskeletal and connective tissue disorders	
Back pain	4 (0.57%)
Bursitis	1 (0.14%)
Cervical spinal stenosis	1 (0.14%)
Intervertebral disc protrusion	7 (1.00%)
Osteitis	1 (0.14%)
Osteoarthritis	1 (0.14%)
Rotator cuff syndrome	1 (0.14%)
Sacral pain	1 (0.14%)
Synovitis	1 (0.14%)
Tendonitis	1 (0.14%)
Vertebral osteophyte	1 (0.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Breast cancer	2 (0.29%)
Cholangiocarcinoma	1 (0.14%)
Prostate cancer	1 (0.14%)
Nervous system disorders	
Cerebellar atrophy	1 (0.14%)

Cerebrospinal fluid leakage	1 (0.14%)
Headache	1 (0.14%)
Hypoaesthesia	1 (0.14%)
Migraine	2 (0.29%)
Multiple sclerosis	1 (0.14%)
Nerve compression	1 (0.14%)
Presyncope	1 (0.14%)
Syncope	1 (0.14%)
Pregnancy, puerperium and perinatal conditions	
Abortion spontaneous	2 (0.29%)
Ectopic pregnancy	1 (0.14%)
Retroplacental haematoma	1 (0.14%)
Psychiatric disorders	
Depression	5 (0.71%)
Depression suicidal	1 (0.14%)
Major depression	1 (0.14%)
Panic attack	1 (0.14%)
Suicide attempt	2 (0.29%)
Renal and urinary disorders	
Nephrolithiasis	1 (0.14%)
Renal colic	2 (0.29%)
Ureterolithiasis	1 (0.14%)
Reproductive system and breast disorders	
Benign prostatic hyperplasia	1 (0.14%)

Endometriosis	2 (0.29%)
Ovarian cyst	1 (0.14%)
Uterine prolapse	1 (0.14%)
Vaginal haemorrhage	1 (0.14%)
Skin and subcutaneous tissue disorders	
Psoriasis	1 (0.14%)
Vascular disorders	
Circulatory collapse	1 (0.14%)
Hypertension	1 (0.14%)
Raynaud's phenomenon	1 (0.14%)

Other (Not Including Serious) Adverse Events

Time Frame	From first dose of study treatment in the Open-label Treatment Epoch of this study to 8 weeks after last dose (up to 132 weeks).
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Erenumab N = 701
Arm/Group Description	Erenumab dose could be adjusted from 70 mg to 140 mg or vice versa at the discretion of the physician at any scheduled study visit.
Total # Affected by any Other Adverse Event	514
Total # at Risk by any Other Adverse Event	701
Ear and labyrinth disorders	
Vertigo	25 (3.57%)
Gastrointestinal disorders	
Abdominal pain upper	15 (2.14%)
Constipation	103 (14.69%)
Diarrhoea	17 (2.43%)
Nausea	34 (4.85%)
General disorders and administration site conditions	
Chills	20 (2.85%)
Fatigue	61 (8.70%)
Pyrexia	20 (2.85%)
Infections and infestations	
COVID-19	242 (34.52%)
Cystitis	23 (3.28%)
Nasopharyngitis	134 (19.12%)
Tonsillitis	18 (2.57%)
Urinary tract infection	18 (2.57%)

Injury, poisoning and procedural complications	
Immunisation reaction	43 (6.13%)
Post vaccination fever	15 (2.14%)
Procedural pain	16 (2.28%)
Musculoskeletal and connective tissue disorders	
Arthralgia	33 (4.71%)
Back pain	42 (5.99%)
Muscle spasms	15 (2.14%)
Osteoarthritis	17 (2.43%)
Pain in extremity	29 (4.14%)
Nervous system disorders	
Dizziness	24 (3.42%)
Headache	42 (5.99%)
Migraine	43 (6.13%)
Psychiatric disorders	
Depression	39 (5.56%)
Respiratory, thoracic and mediastinal disorders	
Cough	18 (2.57%)
Oropharyngeal pain	20 (2.85%)
Skin and subcutaneous tissue disorders	
Alopecia	28 (3.99%)
Pruritus	18 (2.57%)

Vascular disorders	
Hypertension	46 (6.56%)

Conclusion:

The results provide additional data and insights supporting the long-term tolerability and safety of erenumab-treated migraine patients in Germany.

Thus, the results contribute to the understanding of monoclonal antibody-based migraine prophylaxis.

Date of Clinical Trial Report

13-Dec-2023