A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients with Inadequate Response to Prior Preventive Treatments

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON46819

Source
ToetsingOnline

Brief title
TEA48EUC-481EUC / FOCUS

Condition

- Headaches

Synonym
Migraine

Research involving
Human

Sponsors and support

Primary sponsor: TEVA Pharma
Source(s) of monetary or material Support: Teva Branded Pharmaceutical Products R&D Inc.

Intervention

Keyword: Fremanezumab, Migraine, Placebo, Prohylactic

Outcome measures

Primary outcome

The primary efficacy endpoint is the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab

Secondary outcome

The secondary endpoints are as follows:

* proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of fremanezumab

* mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of fremanezumab

* mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab

* proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 4-week period after the 1st dose of fremanezumab
* mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12 week period after the 1st dose of fremanezumab
* mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of fremanezumab

Secondary safety/tolerability endpoints:
* occurrence of adverse events throughout the study
* clinical laboratory (serum chemistry, hematology, coagulation and urinalysis) test results at specified time points
* vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: In addition, oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity
* 12-lead ECG findings at specified time points
* use of concomitant medication for adverse events during the study
* number (%) of patients who did not complete the study due to adverse events
* clinically significant changes in physical examinations, including body weight
* occurrence of severe hypersensitivity/anaphylaxis reactions

* suicidal ideations and behaviors as measured by the eC-SSRS

Study description

Background summary

as nausea (sensation of unease and discomfort in the stomach with an involuntary urge to vomit), photophobia (discomfort or pain in the eyes due to exposure to normal levels of light) or phonophobia (dislike or intolerance of normal levels of sound). The most common form of migraine is referred to as episodic migraine. However, 3% to 6% of individuals with episodic migraine evolve, in any given year, to a more disabling condition called chronic migraine. A considerable number of individuals with chronic migraine experience daily or almost daily headaches and, therefore, face considerable impact to their quality of life.

Fremanezumab is an investigational drug, which means that the drug has not yet been approved as a standard drug by the regulatory authorities in The Netherlands.

The purpose of this research study is to measure how effective and how safe the study drug called fremanezumab is in the prevention of migraine in patients who did not respond to prior migraine preventive treatments (preventive treatment consists of measures taken in order to stop the occurrence of the migraine attacks, or to make these attacks less frequent and/or severe).

Study objective

The primary objective of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo

The secondary objective of the study is to further evaluate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo

A secondary objective of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult patients with migraine with inadequate response to 2 to 4 classes of prior preventive treatments as compared with placebo

Study design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, study with an open-label period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab compared with placebo in patients with CM and EM with inadequate response to prior preventive treatments.

The study will consist of a screening visit, a run-in period (28 days), a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period, and a follow-up visit 6.0 months after the last dose of fremanezumab for ADA blood sample collection.

At the end of the open-label treatment period (4 weeks after the last dose) an end of treatment study visit (visit 8) will be scheduled and patients should return to the care of their treating physicians. Patients should be treated with standard of care after withdrawal from or termination of the 24 week treatment period/study, as appropriate.

Intervention

Double-blind period
At the baseline visit (visit 2), patients will be randomly assigned to a treatment group with fremanezumab (2 different dose regimens) or placebo in a 1:1:1 ratio as follows:
* For patients with CM:
* sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
* sc administration of 675 mg of fremanezumab at visit 2 followed by monthly sc administration of of matching placebo for 2 months or
* 3 monthly doses of matching placebo
* For patients with EM:
* sc administration of fremanezumab at 225 mg plus 2 matching placebo injections as first dose followed by monthly sc administration of 225 mg of fremanezumab for 2 months or
* sc administration of fremanezumab at 675 mg as first dose followed by monthly sc administration of matching placebo for 2 months or
* 3 monthly doses of matching placebo

Open-label period
After visit 4, all patients completing the double-blind period will enter the open-label period. All patients (CM and EM) will receive sc 225 mg of fremanezumab monthly for 3 months. (visits 5, 6, and 7).

Study burden and risks

Risks associated with the study drug (fremanezumab)
Like all medicines, the study drug (fremanezumab) can cause side effects,

although not everybody experiences them. The possible discomforts, side effects and risks related to fremanezumab treatment are not all known yet. Based on previous studies, the study drug is generally well tolerated.

This section describes the most frequent side effects which occurred in patients who were treated with fremanezumab. This list is based on a total of 366 patients with migraine who received at least 1 dose of study medication sub-cutaneously (under the skin).

Common risks (recorded in more than 1 in 100 patients and less than 1 in 10 patients)
o injection site erythema (redness of the skin that is often a sign of infection or inflammation)
injection site pain
o injection site pruritus (itchiness)

Uncommon and rare risks (Recorded in more than 1 in 1000 patients and less than 1 in 100 patients)
o injection site dermatitis (inflammation of the skin)
o drug hypersensitivity (increased sensitivity to the study drug)
Other reported side effects were headache, back pain, and upper respiratory tract infection. Potential risks of taking study drug include perivascular inflammation, development of antidrug antibodies (ADAs), raised liver enzymes, and cardiovascular effects (e.g. on blood pressure, heart rate).

Taking certain other medicines together with study drug may increase the chance of unwanted effects. The risk will depend on how much of each medicine you take every day, and on how long you take the medicines together. If your study doctor instructs you to take these medicines together on a regular basis, follow his or her directions carefully. Please inform your study doctor in case you took any other medicines apart from what your study doctor instructed you to take.

Risks associated to study related assessments
Blood sample collection: A needle is inserted into a vein in your arm and a small blood sample is drawn. Although one blood draw is usually sufficient, a second one may be necessary if the first is not successful. Collecting blood samples may cause fainting and some pain and/or bruising at the site on your arm where the blood was taken. In rare occasions, infection may occur.

Subcutaneous Injections: Injections to the skin may be less convenient than some other forms of treatment, such as oral medications. In addition, injections may cause momentary discomfort and other local symptoms, such as bleeding, bruising, and, rarely, infection and swelling at the injection site.

Unknown risks
There may be risks or side effects related to the study drug or other study

procedures that are unknown at this time. Let your study doctor know if you experience any side effects, even those which are not mentioned in this Participant Information Sheet and Informed Consent Form.

Contacts

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Scientific
TEVA Pharma

Moores Road 41
Frazer, Pennsylvania 19355
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

a. The patient is capable of giving signed informed consent
b. Male or female patient aged 18 to 70 years, inclusive.
c. The patient has a diagnosis of migraine with onset at *50 years of age.
d. The patient is in good health in the opinion of the investigators as determined by medical history, physical examination, laboratory tests, and ECG.
e. Body weight greater than 45 kg and body mass index (BMI) within the range 17.5 to 34.9 kg/m2 (inclusive).

f. The patient has a history of migraine (according to ICHD-3 criteria [IHS 2013]) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for *12 months prior to screening.
g. The patient fulfills the following criteria for CM or EM in prospectively collected baseline information during the 28-day run-in period:
For patients with CM:
* - Headache occurring on *15 days
- On *8 days, fulfilling any of the following:
* ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura
* ICHD-3 criteria B and C for 1.2 Migraine with aura
* Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
* The patient used a triptan or ergot derivative to treat an established headache
For patients with EM:
-Headache occurring on *6 days but <15
-On *4 days, fulfilling any of the following:
* ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura
* ICHD-3 criteria B and C for 1.2 Migraine with aura
* Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
* The patient used a triptan or ergot derivative to treat an established headache
h. At the time of screening, the patient must have documented inadequate response to 2 to 4 classes of prior preventive migraine medications (as defined in Appendix H) within the past 10 years (in medical chart or by treating physician*s confirmation; see Appendix I for acceptable documentation of previous treatment failure). Inadequate response to prior preventive migraine medications (including valproic acid) is defined as: no clinically meaningful improvement per treating physician*s judgment, after at least 3 months of therapy at a stable dose considered appropriate for migraine prevention according to accepted country guidelines, or when treatment has to be interrupted because of adverse events that made it intolerable for the patient, or the medication (as defined in Appendix H) is contraindicated or unsuitable for the prophylactic treatment of migraine for the patient. The 3- month period does not apply if the drug is intolerable or contraindicated. If onabotulinumtoxinA is the previous preventive medication, at least 2 sets of injections and 3 months must have passed since the last set of injections prior to the screening visit.
i. The patient agrees not to initiate any preventive migraine medications (as defined in Appendix H) during the run-in period double-blind treatment periodand open-label period. At the screening visit, at least 5 half-lives of these medications must have passed since the patient has been on any migraine preventive medication as defined in Appendix H.
j. Other prescription medications not in Appendix H must have been on stable doses for at least 2 months at the screening visit with no expectation to change during the double-blind treatment period of the study.
k. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on a minimum of 24 days cumulative during the run-in period (~85% diary compliance).
l. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (*-HCG) test at screening, are sterile, or postmenopausal. Definitions of sterile

and postmenopausal are given in Appendix E.
m. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study and the follow-up period (ie, starting at screening) and for 6.0 months after discontinuation of IMP (for details of WOCBP, sterile, and
postmenopausal women, see Appendix E).
n. Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, acceptable birth control methods for the duration of the study and for 6.0 months after discontinuation of the IMP.
o. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period and to return to the clinic for the follow-up evaluations, as specified in this protocol.

Exclusion criteria

a. At time of screening visit, patient is receiving any preventive migraine medications, regardless of the medical indication (as defined in Appendix H) for more than 5 days and expects to continue with these medications
b. Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit
c. Patient uses medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine [Fiorinal®, Actavis plc], butalbital/paracetamol/caffeine [Fioricet®, Cardinal Health], or any other combination containing butalbital) on more than 4 days during the run-in period for the treatment of migraine or for any other reason
d. Patient has used an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening
e. Patient uses triptans/ergots as preventive therapies for migraine
f. Patient uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (eg, 81 mg) used for cardiovascular disease prevention is allowed
g. Patient suffers from unremitting headaches, defined as having headaches for more than 80% of the time he/she is awake, and less than 4 days without headache per month. Daily headache is acceptable if patient has headaches 80% or less of the time he/she is awake on most days
h. Patient has a clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease that, in opinion of investigator, could jeopardize or would compromise the patient*s ability to participate in this study
i. Evidence or medical history of clinically significant psychiatric issues that, in opinion of investigator, could jeopardize or would compromise patient*s ability to participate in this study including major depression, panic disorder, or generalized anxiety disorder, any suicide attempt in the past or suicidal ideation with a specific plan the past two years prior to screening or current suicidal ideation as measured by eC-SSRS

j. History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g., cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism
k. History of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection
l. Past or current history of cancer, except for appropriately treated non-melanoma skin carcinoma in last 5 years
m. Pregnant or lactating female patients or female patients who plan to become pregnant during the study
n. Participation in clinical study of a new chemical entity or a prescription medicine within 2 months before screening (or 3 months in case of biologics if the half-life of the biologics is unknown) or 5 half-lives, whichever is longer, or is currently participating in another study of an IMP (or medical device)
o. Any prior exposure to a monoclonal antibody targeting the CGRP pathway (such as AMG 334, ALD304, LY2951742, or fremanezumab)
p. Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator
q. Any finding that, in judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation)
r. Hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) >1.5 × the upper limit of the normal (ULN) range after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy*s law at screening
s. Serum creatinine >1.5 × the ULN, clinically significant proteinuria, or evidence of renal disease at screening
t. Patient has history of alcohol abuse during 2 years prior to screening
u. Patient has history of drug abuse during past 2 years or drug dependence during past 5 years
v. Patient cannot participate or successfully complete study, in opinion of their healthcare provider or investigator, for any of the following reasons: -mentally or legally incapacitated or unable to give consent for any reason, -in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution, -unable to be contacted in case of emergency, -has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in study
w. Patient is a study center or sponsor employee who is directly involved in study or the relative of such an employee
x. Patient has been previously screen failed for study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-07-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fremanezumab
Generic name:	TEV-48125

Ethics review

Approved WMO

Date:	28-11-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	19-03-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002441-30-NL
CCMO	NL62917.058.17