A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Episodic Cluster Headache

Published: 07-02-2017
Last updated: 13-04-2024

The primary objective of this study is to demonstrate the efficacy of fremanezumab in the prevention of ECH in adult patients. The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the weekly average number...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON47278

Source
ToetsingOnline

Brief title
TV48125-CNS-30056

Condition

- Headaches

Synonym
Cluster Headache

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: Episodic Cluster Headache, Placebo, Prevention, TEV-48125

Outcome measures

Primary outcome

* the mean change from baseline (run-in period) in the weekly average

number of cluster headache (CH) attacks during the 4-week period after

administration of the first dose of the investigational medicinal product

(IMP), ie, based on week 0 to 4 data

* the proportion of patients with a *50% reduction from baseline (run-in

period) in the weekly average number of CH attacks during the 4 week period

after the first dose of the IMP, ie, based on week 0 to 4 data

* the mean change from baseline (run-in period) in the number of CH attacks

during the 12 week period after administration of the first dose of the IMP,

ie, based on week 0 to 12 data

* the mean change from baseline (run-in period) in the number of CH attacks

during the 4 week period after administration of the third dose of the IMP, ie,

based on week 8 to 12 data

* the mean change from baseline (run-in period) in the weekly average number of days with use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12 week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data

* the mean change from baseline (run-in period) in the weekly average number of days oxygen is used to treat ECH during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data

* assessment of patient*s perceived improvement, as measured by the Patient-Perceived Satisfactory Improvement (PPSI) at 1, 4, 8, and 12 weeks after administration of the first dose of the IMP relative to baseline (day 0)

Secondary outcome

* occurrence of adverse events throughout the study

* clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at each visit

* vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: Oxygen saturation will be measured in cases of suspected anaphylaxis and severe hypersensitivity. Respiratory rate will also be measured in these cases but not as a standard vital sign.

* 12 lead electrocardiogram (ECG) findings at screening, baseline, and week 12

* use of concomitant medication during the study

* clinically significant changes in physical examinations, including body weight

* injection site reaction (ie, erythema, induration, and ecchymosis) and

injection site pain assessments

* occurrence of hypersensitivity/anaphylaxis reactions

* suicidal ideation and behavior as measured by the electronic Columbia Suicide

Severity Rating Scale (eC-SSRS)

Study description

Background summary

This is a 13-week study to evaluate the efficacy and safety of 2 dose regimens of fremanezumab versus placebo in adult patients for the prevention of ECH. Patients who provide written informed consent and complete a screening visit (visit 1) will enter a run-in period lasting at least 1 week (+3 days) during which they will enter baseline CH attack information into an electronic diary device daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]), and patients who continue to meet eligibility requirements will be randomized to receive test IMP (fremanezumab 900-mg iv or 675-mg sc followed by fremanezumab or placebo 225 mg sc monthly) or placebo IMP (placebo iv and sc followed by single placebo doses sc monthly). An EOT visit will occur approximately 4 weeks after the administration of the last dose of IMP to evaluate ADAs, fremanezumab concentrations, biomarkers, and safety. Efficacy will be evaluated using CH attack data entered daily throughout the treatment period in an electronic diary and administration of questionnaires to evaluate CH-related disability, change in quality of life, health status, and satisfaction with treatment. The safety of fremanezumab in patients with CH will be evaluated through adverse event and concomitant medication inquiries, ECGs, vital signs measurements, clinical laboratory tests, physical examinations, injection site reaction/pain assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. In addition, blood will be collected for pharmacokinetics, immunogenicity, biomarker, and pharmacogenomics (unless not allowed per local regulation) analyses, and urine will be collected for biomarker analysis.

Study objective

The primary objective of this study is to demonstrate the efficacy of fremanezumab in the prevention of ECH in adult patients.
The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the weekly average number of cluster headache (CH) attacks

during the 4-week period after administration of the first dose of the IMP, ie, based on week 0 to 4 data.
The secondary efficacy endpoints to further demonstrate efficacy are:
* the proportion of patients with a *50% reduction from baseline (run-in period) in the weekly average number of CH attacks during the 4 week period after the first dose of the IMP, ie, based on week 0 to 4 data
* the mean change from baseline (run-in period) in the number of CH attacks during the 12 week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
* the mean change from baseline (run-in period) in the number of CH attacks during the 4 week period after administration of the third dose of the IMP, ie, based on week 8 to 12 data
* the mean change from baseline (run-in period) in the weekly average number of days with use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12 week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
* the mean change from baseline (run-in period) in the weekly average number of days oxygen is used to treat ECH during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
* assessment of patient*s perceived improvement, as measured by the Patient-Perceived Satisfactory Improvement (PPSI) at 1, 4, 8, and 12 weeks after administration of the first dose of the IMP relative to baseline (day 0)

A secondary objective of this study is to evaluate the safety of fremanezumab in adult patients with ECH.
The secondary safety endpoints are as follows:
* occurrence of adverse events throughout the study
* clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at each visit
* vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: Oxygen saturation will be measured in cases of suspected anaphylaxis and severe hypersensitivity. Respiratory rate will also be measured in these cases but not as a standard vital sign.
* 12 lead electrocardiogram (ECG) findings at screening, baseline, and week 12
* use of concomitant medication during the study
* clinically significant changes in physical examinations, including body weight
* injection site reaction (ie, erythema, induration, and ecchymosis) and injection site pain assessments
* occurrence of hypersensitivity/anaphylaxis reactions
* suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

Study design

This is a 13 week, multicenter, randomized, double-blind, double-dummy,

placebo-controlled, parallel group study to compare the efficacy and safety of 2 dose regimens of fremanezumab versus placebo in adult patients for the prevention of ECH. The study will consist of a screening visit, a run in period lasting at least 1 week (+3 days), and a 12-week double blind treatment period. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.
Patients will complete a screening visit (visit 1) after providing written informed consent, and eligible patients will enter a run-in period lasting at least 1 week (+3 days) during which they will enter baseline CH attack information into an electronic diary device daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]). Patients who had at least 7 CH attacks during the run-in period and who continue to meet eligibility criteria (including entry of CH attack information in an electronic diary demonstrating compliance for 85% of days during the run-in period) will be randomly assigned at visit 2 (week 0) in a 1:1:1 ratio to 1 of 3 treatment groups.

Intervention

Patients will complete a screening visit (visit 1) after providing written informed consent, and eligible patients will enter a run-in period lasting at least 1 week (+3 days) during which they will enter baseline CH attack information into an electronic diary device daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]). Patients who had at least 7 CH attacks during the run-in period and who continue to meet eligibility criteria (including entry of CH attack information in an electronic diary demonstrating compliance for 85% of days during the run-in period) will be randomly assigned at visit 2 (week 0) in a 1:1:1 ratio to 1 of 3 treatment groups.

In order to maintain blinding throughout the study, the number of infusions and injections at each visit will be the same for all patients regardless of the treatment group to which they are randomized. Thus, all patients will receive an iv infusion of test IMP or placebo IMP followed by 3 sc injections of test IMP or placebo IMP at visit 2 (week 0), and all patients will receive single sc injections of test IMP or placebo IMP at visits 3 and 4 (weeks 4 and 8, respectively). Patients will also return for an end of treatment (EOT) visit, approximately 4 weeks after the administration of the last dose of IMP, in order to evaluate ADAs, fremanezumab concentrations, biomarkers, and safety assessments.

The fremanezumab doses, regimens, and routes of administration to be evaluated in this double blind, double-dummy, placebo-controlled study were selected on the basis of 3 key factors. First, simulations suggest that Cmax is the most significant pharmacokinetic parameter in the efficacy of fremanezumab (in migraine). As CH is considered one of the most severe forms of pain a person can experience, treatments that provide quick and lasting relief (ie, for the

duration of the cluster period) are a priority for this patient population. Second, the biological nature of the disease mandates the need for any treatment to desensitize the third order neuron, not the second (as is the case in migraine), suggesting that high levels of blockade at the first neuron would be necessary. Third, the favorable safety profile of the drug and calculated safety margins based modelling and simulations, as well as clinical and nonclinical safety data on exposure, suggest that the proposed doses, regimens, and routes of administration will not present any safety concerns.

In the current study, high doses are planned for the first dose (900 mg iv or 675 mg sc) in order to provide a rapid response, especially following iv infusion where higher peak plasma concentrations (Cmax) generally occur at or shortly after the end of infusion (median tmax values of 1.0 to 5.0 hours after starting the iv infusion) compared with 96 to 108 hours postdose for sc injections. The 2 forms of loading dose will provide data to confirm the benefit of either the iv or sc as loading dose. Monthly doses of fremanezumab at 225 mg sc were added to the initial dose of 900 mg iv for maintenance of efficacy. Based on modelling, the inclusion of a loading dose should allow patients to reach steady state faster. The dose of 675 mg sc quarterly in this ECH population will allow for the evaluation of a single treatment dose taking into account the periods of remission seen with this CH form.

Study burden and risks

Risks associated to the study drug.
Like all medicines, 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. The study drug is generally well tolerated. A total of 484 subjects/patients (118 healthy subjects and 366 patients with migraine) have been treated with at least 1 dose of TEV-48125 in the past in clinical trials. Also there are 5 other ongoing trials with the study drug for migraines. This section describes the most frequent side effects which occurred in subjects who were treated with fremanezumab.

- Injection site disorders/reactions in some of the patients that received fremanezumab as subcutaneous injections:
* injection site erythema (redness of the skin that is often a sign of infection or inflammation), (15 patients on fremanezumab versus 5 patients on placebo).
* injection site pain (38 patients on fremanezumab versus 13 patients on placebo).
* injection site pruritus (itchiness), (7 patients on fremanezumab versus 0 on placebo).
* injection site dermatitis (inflammation of the skin), (3 patients on fremanezumab versus 0 on placebo)
* drug hypersensitivity (was observed in one patient treated with intravenous administration (infusion related reaction) and one patient with subcutaneous

injection of fremanezumab

- Infusion-related reaction for patients treated with intravenous fremanezumab:
* administration site pain
* infusion-related reaction

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, other).

Taking certain other medicines together with fremanezumab 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.

Like in the case of infusion of any drug of this class, there is the infusion associated risk of fever, headache, nausea, vomiting or hypotension.

Risks associated to blood drawn:
Blood samples will be collected during this study. A needle is inserted into a vein in your arm and a small blood sample is withdrawn. 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.

Your or your partner*s pregnancy
Information for women:
The risks of taking TEV-48125 to pregnant women or an unborn baby are unknown. For this reason, women must have a pregnancy test before the study starts and again just before receiving TEV-48125. Women who are pregnant or breast-feeding cannot be in this study. Women must not become pregnant during this study. If you are a woman of childbearing potential, you must use an effective form of birth control during this study and continue until 7,5 months after the last dose.
Some drugs (e.g., antibiotics) may interact with hormonal contraceptives, making them not work properly. Please inform your study doctor of all other medications you are taking.

Information for men:
Men should keep in mind that their partner must not become pregnant during the study. Inform your partner about this.
The effects of the study drug on the male reproductive system are not known at this time, and contraceptive methods should be used throughout the study and

for 7,5 months after completion of the study.

Contacts

Public
TEVA Pharma

Moores Road 41
Frazer, Pennsylvania 19355
US
Scientific
TEVA Pharma

Moores Road 41
Frazer, Pennsylvania 19355
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

a. Patients are capable of giving signed informed consent as described in Appendix D which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
b. The patient is a man or woman 18 to 70 years of age, inclusive.
c. The patient has a history of ECH according to ICHD-3 beta criteria (Headache Classification Committee of the IHS 2013) for *12 months prior to screening including the following:
* Attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15 to 180 minutes and occurring from

once daily every other day to 8 times a day for more than half of the time when the disorder is active
* The pain is associated with at least 1 of the following symptoms or signs: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis and/or ptosis and/or eyelid edema, and/or sense of restlessness or agitation.
CH attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 1 month.
d. CH attacks of a new cluster cycle have started within 2 weeks (14 days, inclusive) prior to screening and, based on the patient*s previous medical history, it is expected that the patient*s CH attacks will continue for *6 weeks after the screening visit.
e. The patient has a total body weight of *45 kg
f. The patient is not using or using * 2 concomitant medications that are commonly prescribed as preventive treatments for CH (Appendix H), regardless of the indication for which the medication was prescribed. Patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.
g. If a patient is receiving Botox, it should be in a stable dose regimen, considered as having *2 cycles of Botox prior to screening. The patient should not receive Botox during the run-in period up to the evaluation period (4 weeks) where the primary endpoint is evaluated.
h. The patient has demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on 85% of days during the run-in period.
i. The patient has at least 7 CH attacks during the run-in period.
j. The patient is in good health in the opinion of the investigator as determined by a medical and psychiatric history; medical examination; 12-lead ECG; and serum chemistry, hematology, coagulation, and urinalysis.
k. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (*-HCG) test at screening, are sterile or postmenopausal, and are not lactating. Definitions of
sterile and postmenopausal are given in Appendix E.
l. 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 (ie, starting at screening) and for 7.5 months after discontinuation of IMP.
m. 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 agree to use, together with their female partners, acceptable birth
control methods for the duration of the study and for 7.5 months after discontinuation of the IMP. Definitions of women of non-childbearing potential, sterile women, and postmenopausal women; male
contraception; and highly effective and acceptable birth control methods including examples are given in Appendix E.
n. 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. The patient has used systemic steroids for any reason (including treatment of the current CH cycle) within *7 days prior to screening.
b. The patient reports using butalbital on more than 7 days during the 4 weeks prior to screening or using butalbital on more than 3 days during the screening/run-in period.
c. The patient reports using opioids on more than 15 days during the 4 weeks prior to screening or using opioids on more than 4 days during the screening/run-in period.
d. The patient has used an intervention/device (eg, scheduled nerve blocks) for headache during the 4 weeks prior to screening.
e. The patient has clinically significant hematological, renal, endocrine, immunologic, pulmonary,
gastrointestinal, genitourinary, cardiovascular, neurologic, hepatic, or ocular disease at the discretion of the investigator.
f. The patient has evidence or medical history of clinically significant psychiatric issues determined at the discretion of the investigator.
g. The patient has a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.
h. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, 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.
i. The patient has a past or current history of cancer or malignant tumor in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.
j. The patient is pregnant or lactating.
k. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies.
l. The patient has participated in a clinical study of a new chemical entity or a prescription medicine within 2 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer.
m. The patient has participated in a clinical study of a monoclonal antibody within 3 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer, unless it is
known that the patient received placebo during the study.
n. The patient has a history of prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or fremanezumab). If patient has participated in a clinical study with any of these monoclonal antibodies, it has to be confirmed that the patient received placebo in order to be eligible for this study).
o. The patient has any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.
p. The patient has any finding that, in the 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).
q. The patient has hepatic enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) >1.5 × the upper limit of normal (ULN) range after

confirmation in a repeat test, or the patient has suspected hepatocellular damage that fulfills criteria for Hy*s law at screening.
r. The patient has serum creatinine >1.5 × the ULN or evidence of clinically significant renal disease in the judgement of the investigator.
s. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the 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 the study
t. The patient is an employee of the sponsor/participating study center who is directly involved in the study or is the relative of such an employee.
u. The patient has an active implant for neurostimulation used in the treatment of CH.
v. The patient is a member of a vulnerable population (eg, people kept in detention).
w. The patient has a history of alcohol and/or drug abuse that in the investigator*s opinion could interfere with the study evaluations or the patient*s safety.

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:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	07-02-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-07-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-09-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-10-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-10-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	05-07-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-10-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2016-003278-42-NL

Register	ID
CCMO	NL59616.058.17