A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

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

Summary

ID

NL-OMON49442

Source
ToetsingOnline

Brief title
TV48125-CNS-30058

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: Cluster Headache, Long-Term Safety, TEV-48125

Outcome measures

Primary outcome

As of 15 June 2018, only patients from the ECH study (Study TV48125 CNS 30056) will enroll in this study for active treatment. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. Data from CCH patients enrolled prior to 15 June 2018 will be evaluated per all objectives of this study.

Safety endpoints are as follows:

* occurrence of adverse events throughout the study

* changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results

* changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in vital signs (pulse, systolic and diastolic blood pressure, and oral temperature) measurements

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.

* abnormal standard 12-lead electrocardiogram (ECG) findings

* clinically significant changes in physical examination, including body weight

* occurrence of injection site reactions (ie, erythema, induration, and

ecchymosis) and injection site pain

* occurrence of anaphylaxis and hypersensitivity reactions

* use of concomitant medications during the study

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

Severity Rating Scale (eC-SSRS)

Secondary outcome

not applicable

Study description

Background summary

This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumabTEV-48125 in adult patients with CH. Patients who complete the pivotal studies and enroll into the current study (at visit 1 [week 0]) will visit the investigational center approximately every 4 weeks for 36 weeks for IMP administration (fremanezumab at 675 mg sc quarterly, 225 mg sc monthly, or a loading dose of 675 mg sc followed by 225 mg sc monthly), safety assessments, and blood and urine collections for pharmacokinetics, immunogenicity (ADAs), and biomarker analyses. An EOT visit will occur approximately 4 weeks after administration of the last dose of IMP. Patients will return to the investigational center for a follow-up visit to evaluate ADAs, biomarkers, and safety (adverse events and concomitant medications) approximately 7.5 months after the last dose of IMP.

The long-term 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 assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. Efficacy will be evaluated using CH attack data

entered daily throughout the treatment period in an electronic diary and administration of questionnaires to evaluate change in quality of life, satisfaction with treatment and health status. In addition, blood will be collected for pharmacokinetics, immunogenicity, and biomarkers, (blood for pharmacogenomics is collected during the pivotal studies), and urine will be collected for biomarker analysis.

Study objective

As of 15 June 2018, only patients from the ECH study (Study TV48125 CNS 30056) will enroll in this study for active treatment. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. Data from CCH patients enrolled prior to 15 June 2018 will be evaluated per all objectives of this study.

The primary objective of this study is to evaluate the long term safety of fremanezumab in adult patients with CH.
Safety endpoints are as follows:
* occurrence of adverse events throughout the study
* changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results
* changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in vital signs (pulse, systolic and diastolic blood pressure, and oral temperature) measurements
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.
* abnormal standard 12-lead electrocardiogram (ECG) findings
* clinically significant changes in physical examination, including body weight
* occurrence of injection site reactions (ie, erythema, induration, and ecchymosis) and injection site pain
* occurrence of anaphylaxis and hypersensitivity reactions
* use of concomitant medications during the study
* suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

Study design

This is a 68-week extension study to evaluate the long term safety and efficacy of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).
Upon completion of the final study assessments, early withdrawal from the study or discontinuation for any reason, patients will be offered the opportunity to

enter a 32-week long term safety study (as described in Study TV48125-CNS-30058) for safety and ADA evaluation without additional dosing. Patients who satisfactorily complete the study may be offered to enroll the long-term safety study TV 48125-CNS-30058 for 68 weeks (as described in this study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In any case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate.
Prior to 15 June 2018, up to 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125 CNS 30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study as summarized in Table 1. After 15 June 2018, only patients who participated in the ECH study (Study TV48125 CNS 30056) will be enrolled in this study for active treatment. At the time of unblinding the treatment code in Study TV48125 CNS 30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125 CNS 30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

Intervention

Female and male patients with CCH and ECH who complete the pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) may enter this long term safety study if they provide informed consent and meet the inclusion/exclusion criteria. In addition, patients who do not complete the pivotal efficacy studies, and patients who complete the pivotal efficacy studies but do not wish to continue treatment during this long term safety study, may enroll in this study for the purpose of evaluating ADAs, fremanezumabTEV-48125 concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months after administration of the last dose of the IMP.

This is a double-blind study; blinding will be retained from the pivotal studies and throughout this long-term safety extension study. Patients will be assigned to treatments as described in Table 1 based on their randomization in the pivotal studies (Studies TV48125-CNS 30056 and TV48125-CNS-30057). Refer to the protocols for the pivotal studies (Studies TV48125 CNS 30056 and TV48125-CNS-30057) for details regarding randomization of patients in this study. After 15 June 2018, only patients who participated in the ECH study (Study TV48125 CNS 30056) will be enrolled for active treatment.

Patients who receive fremanezumab at 225 mg sc monthly after a loading dose of 900-mg intravenously or 675 mg sc or fremanezumab at 675 mg sc quarterly during the pivotal studies will continue receiving the same dose (ie, 225 mg sc monthly or 675 mg sc quarterly depending upon their diagnosis and randomization in the pivotal studies) during this long-term safety extension study. These

dose regimens are expected to maintain steady state at a blood concentration level that will provide clinical efficacy. The doses and dosing regimens also account for the natural history of the 2 forms of CH; patients with ECH are likely to remit after initial treatment whereas CCH patients are continuously inflicted by pain.
Patients who receive placebo during the pivotal studies will be assigned to receive either fremanezumab 675 mg sc quarterly (patients with ECH from Study TV48125-CNS-30056) or a loading dose 675 mg sc followed by monthly fremanezumabTEV-48125 at 225 mg sc monthly (patients with CCH from Study TV48125-CNS-30057). This will provide these patients with the opportunity to receive potential benefit from therapeutic doses including the loading dose of 675 mg sc. After 15 June 2018, only patients who participated in the ECH study (Study TV48125 CNS 30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125 CNS 30057 (ie, never received any study drug) will not be required to complete further safety follow up visits and will be discharged from the study.

When the cluster cycle is almost over in ECH, the number of headache attacks per day start to decrease with associated mild to moderate intensity. Patients often look for preventive options in the very early part of the headache cycle in an attempt to reduce its duration. Equally, when complete remission is achieved patients with ECH consider stopping their medication and thus withdraw from treatment when the cluster period is over (May 2005). Accordingly, continuous long-term treatment in ECH might not be needed as these patients may have long remission periods between the cluster episodes. Patients with CCH may face a different situation, where the remission period is very short (less than a month). These patients might be more inclined to continue with long-term preventive treatment. Thus, the current study will evaluate the concept of intermittent treatment in both ECH and CCH; IMP administration maywill be discontinued in patients with CH remission (defined in ECH as patients with at least 12 successive weeks of no CH attacks at any time after starting IMP and in CCH as patients with at least 24 successive weeks of no CH attacks at any time after starting IMP).

Differentiating between remission periods lasting 12 weeks or less and remission period lasting more than 12 weeks after treatment has been stopped, dictates the need for the administration of a loading dose of fremanezumab at 675 mg sc when remission lasted for more than 12 weeks (as most of the drug is eliminated after 12 weeks). Thereafter, the doses and dosing regimens are identical to those in the pivotal studies for each CH form (ie, 225 mg sc monthly for CCH and 675 mg sc quarterly for ECH). If treatment is stopped and headache attacks restart within 12 weeks of stopping the treatment, patients will proceed with their previous dose, which is expected to re establish efficacy and which maintains the differentiation between the 2 CH forms. After

15 June 2018, only patients who participated in the ECH study (Study TV48125 CNS 30056) will be enrolled for active treatment.

Study burden and risks

Risks associated to the study drug
Like all medicines, TEV-48125 can cause side effects, although not everybody experiences them. The possible discomforts, side effects and risks related to TEV-48125 treatment are not all known yet. The study drug is generally well tolerated. A total of 2269 subjects/patients (256 healthy subjects and 2013 patients with migraine) have been treated with at least 1 dose of TEV-48125 in the past in clinical trials. Also there are other 5 ongoing trials with the study drug for migraines. This section describes the most frequent side effects which occurred in subjects who were treated with TEV-48125.

Injection site disorders/reactions in some of the patients that received TEV-48125 as subcutaneous injections:
* injection site induration (lump under the skin), (292 patients on TEV-48125 versus 113 patients on placebo)
* injection site erythema (redness of the skin that is often a sign of infection or inflammation, (273 patients on TEV-48125 versus 104 patients on placebo).
* injection site pruritus (itchiness), (30 patients on TEV-48125 versus 2 on placebo).
* injection site rash (13 patients on TEV-48125 versus 0 on placebo)

Other reported side effects with highest frequency across all arms were nasopharyngitis (runny nose and sore throat) and upper respiratory tract infection. Potential risks of taking study drug include development of antidrug antibodies (ADAs) and drug hypersensitivity. Drug hypersensitivity was observed in five patients treated with TEV-48125
It is unknown whether taking certain other medicines together with TEV-48125 may increase the chance of unwanted effects. The risk may 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 other medicines together with TEV-48125 on a regular basis, follow his or her directions carefully.

Risks associate 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 a highly 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

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Scientific
TEVA Pharma

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

a. The patient is a male or female and 18 to 70 years of age, inclusive, at the start of the pivotal study.
b. The patient signs and dates the informed consent document.
c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125 CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study. Prior to 15 June 2018, patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125 CNS 30056) will be enrolled for active treatment.
* In addition, patients who do not complete the pivotal efficacy studies, and patients who complete the pivotal efficacy studies but will not continue treatment during this long-term safety study, will be offered to enroll in this study for the purpose of evaluating ADAs and safety (adverse events and concomitant medications) approximately 7.5 months after administration of the last dose of the IMP.
d. Women may be included only if they have a negative beta-human chorionic gonadotropin test at visit 1; are sterile or postmenopausal; and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.
e. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP.
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 administration of IMP.
Definitions of women of non-childbearing potential, sterile and postmenopausal women; male contraception; and highly effective and acceptable birth control methods, including examples, are given in Appendix E.
f. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH (ie, verapamil, topiramate, valproate, lithium, or methysergide) for the duration of this study. Patients must begin tapering these preventive medications as soon as they begin this study. The period of time needed to taper off these medications will be based on the investigator*s medical judgment but should not exceed 1 month from the beginning of participation in this study (Appendix H) (not applicable for patients participating in safety follow up only).
g. 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 (not applicable for patients participating in safety follow-up only).

h. 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 a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.
b. Any finding in the 12-lead ECG performed as part of the EOT visit (visit 5) procedures for the pivotal studies considered clinically significant in the judgment of the investigator
c. 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)
d. Hepatic enzymes (alanine aminotransferase and aspartate aminotransferase) >1.5 × the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy*s law
e. Serum creatinine >1.5 × the ULN or evidence of clinically significant renal disease in the judgment of the investigator
Patients rolling over only for safety follow-up and ADA, who are not receiving study medication, are not required to fulfil all inclusion exclusion criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-04-2018

Enrollment:	20
Type:	Actual

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:	09-11-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	01-12-2017
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:	31-10-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-03-2019
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	EUCTR2016-003172-43-NL
CCMO	NL59625.058.17