A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Chronic Migraine in Pediatric Patients 6 to 17 Years of Age

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Main objective:The primary objective of the trial is to evaluate the efficacy of test investigational medicinal product (IMP) as compared to placebo IMP for the preventive treatment of chronic migraine (CM). Secondary objectives:To evaluate the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Headaches
Study type	Interventional

Summary

ID

NL-OMON56018

Source
ToetsingOnline

Brief title
SPACE

Condition

- Headaches

Synonym
migraine; headache

Research involving
Human

Sponsors and support

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

Intervention

Keyword: chronic migraine, fremanezumab, pediatric

Outcome measures

Primary outcome

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

Secondary outcome

The safety and tolerability endpoints are as follows:

• occurrence of adverse events throughout the trial, including local injection site reaction/pain

• abnormal standard 12-lead electrocardiogram (ECG) findings

• changes from baseline in vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), height, and weight measurements

• changes from baseline in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results

• abnormal physical examination findings

• suicidal ideation and behavior as suggested by the Columbia-Suicide Severity

Rating Scale (C SSRS)

The secondary efficacy endpoints are as follows:

• mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12 week period after the first dose of IMP

• proportion of participants reaching at least 50% reduction inthe monthly average number of migraine days during the 12-week period after the first dose of IMP

• mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of IMP

• mean change from baseline (day 1) in migraine-related disability score, as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, at 12 weeks after administration of the first dose of IMP

• mean change from baseline (day 1) in quality of life, as measured by the Pediatric Quality of Life Inventory (PedsQL), at 12 weeks after administration of the first dose of IMP

• proportion of participants developing ADAs throughout the trial. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA positive participants allows.

Study description

Background summary

Fremanezumab is a humanized immunoglobulin G2 (IgG2) Δa/kappa monoclonal antibody (mAb) derived from a murine precursor. In September 2018, fremanezumab was approved in the United States of America (US) for the preventive treatment of migraine in adults and marketed under the trade name AJOVY®. Fremanezumab has also been approved in the European Union (EU) and a number of countries worldwide. Fremanezumab is a potent, selective calcitonin gene-related peptide (CGRP) binder and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine is unknown, it is believed that blocking CGRP prevents activation of the trigeminal system. Fremanezumab is highly specific for CGRP and does not bind to closely related family members (eg, amylin, calcitonin, intermedin, and adrenomedullin). Two mutations were introduced into the constant region of the fremanezumab heavy chain to limit antibody effector functions. This loss of function prevents fremanezumab from stimulating antibody-dependent cell-mediated cytotoxicity and triggering complement-mediated lysis; these activities can lead to unwanted consequences, such as cell lysis, opsonization, and cytokine release and inflammation.

The safety and tolerability of fremanezumab (intravenous [iv] doses of 0.2 to 2000 mg and subcutaneous [sc] doses of 225 to 900 mg) as well as the pharmacokinetic profile of 225 to 900 mg sc and iv have been well characterized in the Phase 1 development program in adults.
Furthermore, the safety and effectiveness of fremanezumab have been demonstrated in 2 Phase 2b trials and 3 Phase 3 trials in adult participants with migraine. The 2 Phase 2b trials were a randomized, double-blind, placebo-controlled Phase 2b trial of 2 sc dosing regimens of fremanezumab (monthly fremanezumab at 900 mg or fremanezumab at 675 mg followed by monthly fremanezumab at 225 mg) in participants with chronic migraine (CM) and a randomized, double-blind, placebo-controlled Phase 2b trial of 2 sc dosing regimens of fremanezumab (monthly fremanezumab at 675 or 225 mg) in participants with episodic migraine (EM).

Two completed, randomized, double-blind, placebo-controlled Phase 3 trials (Trials TV48125-CNS-30049 in CM and TV48125-CNS-30050 in EM and 1 completed, randomized, double-blind Phase 3 long-term safety trial (Trial TV48125-CNS-30051 in migraine [EM and CM]) were conducted to further evaluate the efficacy, safety, and tolerability of various dose regimens of fremanezumab in the preventive treatment of migraine. Additional trials within the migraine development program of fremanezumab include the completed Phase 3b trial (Trial TV48125-CNS-30068) in participants from the EU and US to evaluate the safety and efficacy of fremanezumab in migraine participants who have failed multiple preventive medications, 2 ongoing Phase 2b/3 trials in Japanese and Korean EM and CM participants (Trials 406-102-00002 and 406-102-00001, respectively), and

1 ongoing long-term safety trial (Trial 406-102-00003) in CM and EM to evaluate the safety and efficacy of fremanezumab. One Phase 4 trial (Trial TV48125-MH-40142) was conducted to evaluate the efficacy and safety of fremanezumab in adult participants with migraine and comorbid major depressive disorder.
The pediatric migraine development program includes a completed Phase 1, single-dose, open-label trial with administration of single sc doses of 75 mg in pediatric participants with migraine 6 to 11 years of age, inclusive (Trial TV48125-CNS-10141). Fremanezumab is further studied for the preventive treatment of persistent posttraumatic headache (PPTH) in 1 Phase 2 trial (Trial TV48125-CNS-20024) that is comparing the efficacy and safety of the sc dose regimen of fremanezumab versus placebo in participants with PPTH. Fremanezumab was being studied for the preventive treatment of cluster headache (CH) in 3 Phase 3 trials: Trial TV48125-CNS-30056 in participants with episodic CH, Trial TV48125-CNS-30057 in participants with chronic CH, and a longterm safety Trial TV48125-CNS-30058 in CH. All 3 trials were terminated by Teva because a prespecified futility analysis showed that the primary endpoint of mean change from baseline in the monthly average number of CH attacks during the 12-week treatment period was unlikely to be met.

Migraine is a prevalent condition characterized by attacks of headache and associated symptoms (such as nausea, photophobia, or phonophobia). Among populations of children of all ages, migraine prevalence ranges from 8% to 11%
The prevalence of migraine is substantially lower among children younger than 7 years, ranging from 1% to 3%
The prevalence of migraine in children younger than 12 years is less than one-third of the prevalence among adolescents
Therefore, the prevalence of migraine increases throughout childhood, with estimates for adolescents comparable to the 12% to 15% prevalence estimates cited for adult populations
Migraine has been classified by headache frequency in the International Classification of Headache Disorders, 3 rd revision (ICHD-3) and is described as EM, which is defined as headaches occurring on less than 15 days per month, and CM, which is defined as headaches on at least 15 days per month for at least 3 months, with the features of migraine on at least 8 days per month
Treatment options for migraine include non-pharmacological biobehavioral strategies and pharmacological strategies. Topiramate is the only migraine preventive medication approved for pediatric populations, but it is not approved in all regions of the EU and is
limited to adolescents ages 12 through 17. Non-pharmacological strategies for adults and children with migraine include sleep hygiene, exercise, dietary modifications, biofeedback, and stress management (. Pharmacologic agents used for the treatment of migraine can be classified as acute (ie, to alleviate the acute migraine attack) or prophylactic (ie,preventing headache recurrence). Preventive therapy is indicated for all individuals with CM and for those with EM that have high frequency of attacks. If given during CM, prophylactic treatments could revert the patients to EM and continue to provide benefit

after remission is achieved. Most specialists require that a child experience a minimum of 1 headache per week or 3 to 4 headaches per month to justify prophylactic medication. Children who report intensive and prolonged headaches (lasting more than 48 hours), even if infrequent, may also be offered prophylactic therapy. It is recommended that an adequate trial of at least 6 to 8 weeks should be sustained before abandoning a treatment. Detailed information on the test investigational medicinal product (IMP) (fremanezumab), nonclinical pharmacokinetics, toxicology studies, and clinical trials/studies are provided in the Investigator*s Brochure (IB).

Study objective

Main objective:
The primary objective of the trial is to evaluate the efficacy of test investigational medicinal product (IMP) as compared to placebo IMP for the preventive treatment of chronic migraine (CM).

Secondary objectives:
To evaluate the safety and tolerability of test IMP in the preventive treatment of CM.
-To further demonstrate the efficacy of test IMP as compared to placebo IMP for the preventive treatment of CM.
-To eevaluate the immunogenicity of test IMP and the impact of antidrug antibodies (ADAs) on clinical outcomes in participants exposed to test IMP.

Study design

This is a 4-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group studytrial to evaluate the efficacy, safety, and tolerability of 2 different doses (dependent on partiecipants* body weight) of subcutaneous (sc) fremanezumabtest investigational medicinal product (IMP) and placebo IMP. Enrollment will include male and female partiecipants (6 to 17 years of age, inclusive). The dose of test IMP will be determined by the participant*s weight at randomization.

The trial consists of a screening visit, a 28-day baseline period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose IMP).

Intervention

Participants will be randomly assigned in a 1:1 ratio between fremanezumabtest IMP and placebo IMP treatment groups:
• monthly sc administration of test IMP
• monthly sc administration of matching placebo IMP

The dose of test IMP to be administered will be determined by the participant*s weight at randomization (visit 2):
• participants weighing >=45.0 kg will receive monthly sc administration of test IMP at 225 mg.
• participants weighing <45.0 kg will receive monthly sc administration of test IMP at 120 mg.

Study burden and risks

Identified Risks:
The identified risks of fremanezumab are the following:
• Injection site induration
• Injection site erythema
• Injection site pruritus
• Injection site rash
• Injection site pain
None of these risks impact the benefit-risk profile.

Mild and moderate drug hypersensitivity events were observed infrequently and with similar incidence in placebo and fremanezumab
in the clinical development program, but no anaphylaxis or severe hypersensitivity reactions were seen. However, it cannot be
excluded that severe events may occur in the future. Additional information regarding benefits and risks to participants may be found
in the IB.

In summary, the benefit and risk assessment for fremanezumab is favorable following review of the observed clinical adult data.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

a. The participants is a male or female between the ages of 6 to 17 years (inclusive) on the day of randomization to test IMP/placebo IMP.
b. The participant*s parent(s) or legal guardian(s) must give written informed consent, and the participant must give assent (in accordance with local regulations).
Note: In some countries, participants aged 15 to 17 years (inclusive) may give written informed consent; however, the participant*s parent(s) or legal guardian(s) must be informed, per local regulations.
c. [Revision 01]The participant has a clinical history of recurrent headache consistent with the diagnosis of migraine for at least 6 months before screening, consistent with ICHD-3 criteria, (Headache Classification Committee of the IHS 2013), and a history of >=15 headache days per month on average during the 3 months prior to screening (visit 1).
d. The participant or parent/caregiver has maintained a prospectively collected headache diary during a 28-day baseline period in which headache days were recorded on 15 or more days, and 8 or more of these headache days had at least 1 of the following migraine characteristics:
* head pain of moderate to severe intensity lasting for 2 or more hours in duration and accompanied by either throbbing quality, predominantly unilateral location, or aggravation with normal activities.
* headache is accompanied by a migraine-associated symptom, such as photophobia, phonophobia, abdominal pain, nausea, or vomiting.
* headache is preceded by an aura, as described by ICHD-3 criteria.
* headache was treated by a nonsteroidal anti-inflammatory drug, paracetamol, triptan, or ergot preparation.
e. This criterion was deleted
f. [Revision 01]Not using migraine preventive medications (listed in Section

13.8) or using no more than 2 migraine preventive medications for migraine or other medical condition, as long as the dose and regimen have been stable for at least 2 months prior to screening (visit 1). A list of migraine preventive medications allowed for any condition for the duration of the trial for approximately 35% of participants
Note: A person is considered to be not using migraine preventive medications (listed in Section 13.8) when at least 5 half-lives have passed since the last use of the medication prior to screening (visit 1) or at least 4 months have passed since the last use of Onabotulinum toxin A or B prior to screening (visit 1). The use of other agents that are not included in Section 13.8 but used for migraine prevention is permitted during the trial; however, these participants will not be counted towards the approximately 35% participant limit threshold.
g. Females who are postmenarchal or >=12 years of age may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at baseline or are sterile.
h. Females who are postmenarchal or >=12 years of age and sexually active must use highly effective birth control methods with their male partners for the duration of the trial (ie, starting at screening) and for 6 months after the last dose of IMP. Males who are sexually active with female partners must use a condom for the duration of the trial and for 6 months after the last administration of IMP.
i. The participant/caregiver has demonstrated compliance with the electronic headache diary during the 28-day baseline period by entry of headache data on a minimum ofn21 out of 28 days (approximately 75% diary compliance).
j. The participant is in good health, as determined by a medical and psychiatric history, medical examination, 12-lead electrocardiogram (ECG), serum chemistry, hematology, coagulation, urinalysis, and serology.
k. The participant/caregiver must be willing and able to comply with trial requirements and return to the clinic as required for the duration of the trial.
l. The participant weighs at least 17.0 kg on the day of randomization to test IMP/placebo IMP.
m. The participant has a body mass index ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.
n. The participant has received all recommended age-appropriate vaccines according to local standard of care and schedule prior to screening.

Exclusion criteria

a. The participant is using medications containing opioids (including codeine) or barbiturates (including Fiorinal ,Fioricet, or any other combination containing butalbital) for the treatment of migraine during the 3 months prior to the day of the screening visit.
b. The participant has used an intervention/device (eg, scheduled nerve block or transcranial magnetic stimulation) for the treatment of migraine or in the

head or neck area for any condition during the 2 months prior to the day of the screening visit.
c. The participant has any clinically significant cardiovascular (including congenital cardiac anomalies or thromboembolic events), endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, renal disease, or complications of an infection, at the discretion of the Investigator.
d. [Revision 01] The participant has a current history of a clinically significant psychiatric condition, at the discretion of the investigator. Any prior history of a suicide attempt, or a history of suicidal ideation with a specific plan within the past 2 years must be excluded.
e. The participant has an ongoing infection or a known history of human immunodeficiency virus (HIV) infection, tuberculosis, Lyme disease, chronic hepatitis B or C, or a known active infection of COVID-19.
f. The participant has a past or current history of cancer.
g. The participant is pregnant or nursing.
h. The participant has a history of hypersensitivity reactions to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis syndrome, or the participant is concomitantly using lamotrigine.
i. The participant has participated in another trial of an IMP (or a medical device) within the 30 days (or 90 days for biologics) or 5 half-lives previous to the day of the screening visit (whichever is longer), or is currently participating in another trial of an IMP (or a medical device).
j. The participant has had exposure to a mAb targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, fremanezumab) during the 6 months previous to the day of the screening visit.
k. Previous participation in the Phase 1 pharmacokinetics trial (Trial TV48125-CNS-10141).
l. In the judgment of the Investigator, the participant has an abnormal finding on the baseline 12-lead ECG considered clinically significant.
m. In the judgment of the Investigator, the participant has a significantly abnormal finding during the 28-day baseline period, including hematology, blood chemistry, coagulation tests, or urinalysis values/findings (abnormal tests may be repeated for confirmation).
n. The participant has hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]) more than 1.5× the upper limitof normal (ULN) during the 28-day baseline period, after confirmation in a repeat test, or suspected hepatocellular damage that fulfills the criteria for Hy*s law.
o. The participant has serum creatinine more than 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate (eGFR) of <75 mL/min/1.73m 2, as calculated by the revised Schwartz formula (eGFR=[0.413×Ht]/serum creatinine), or evidence of renal disease during the 28-day baseline period.
p. The participant has any history of alcohol or drug abuse. The definition of alcohol or drug abuse, including marijuana, is based on the Investigator's

clinical judgement.
q. In the judgment of the Investigator, the participant cannot fully participate in or successfully complete the trial for its full duration for any of the following reasons:
* The participant is mentally or legally incapacitated, or unable to give assent/consent for any reason.
* The participant is in custody due to an administrative or a legal decision or is in residential treatment.
* The participant /caregiver is unable to be contacted in case of emergency.
* The participant has any other condition, which, in the opinion of the Investigator, makes the patient inappropriate for inclusion in the trial.
* The participant is a relative of a trial center or Sponsor employee who is directly involved in the trial.
r. Vulnerable participants (eg, people kept in detention) whose vulnerability is based on a condition other than the age required for trial eligibility.
s. The participant received a live attenuated vaccine (eg, intranasal flu vaccine, and measles, mumps, and rubella vaccine) within the 12-week period prior to screening.
Note: If a medical need arises during the trial, the participant may receive a live attenuated vaccine.
t. The participant has a known hypersensitivity to the active substance or to any of the excipients of the IMP.
u. The participant has a current or past medical history of hemiplegic migraine.

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: Completed

Start date (anticipated):	03-03-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ajovy
Generic name:	fremanezumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2024
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2019-002053-33-NL
ClinicalTrials.gov	NCT04464707
CCMO	NL74045.056.20