A Multicenter, Open-Label Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Monthly Subcutaneous Administration of Fremanezumab for the Preventive Treatment of Episodic and Chronic Migraine in Pediatric Patients 6 to 17 Years of Age

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This study has been transitioned to CTIS with ID 2024-512837-34-00 check the CTIS register for the current data. Main objective:To evaluate the long-term safety and tolerability of subcutaneous test IMP in the preventive treatment of migraine in...

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

Summary

ID

NL-OMON56148

Source
ToetsingOnline

Brief title
TV48125-CNS-30084 (0075/0153)

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 Pharmaceutical Products R&D;Inc.

Intervention

Keyword: fremanezumab, migraine, pediatric

Outcome measures

Primary outcome

Safety:

-Occurrence of adverse events throughout the trial, including local

injection site reactions/pain

-Changes from baseline in clinical laboratory (serum chemistry,

hematology, coagulation, and urinalysis) test results and height and

weight measurements taken at V5, V8, and at the end of treatment

(V11)

-Abnormal standard 12-lead electrocardiogram findings at each trial visit

up to the end of treatment (V11)

-Changes from baseline in vital signs (pulse, systolic and diastolic blood

pressure, temperature, and respiratory rate) at each trial visit up to the

end of treatment (V11)

-Abnormal physical examination findings at trial visits V6, V7, V11, and

V12

-Suicidal ideation and behavior as suggested by the Columbia-Suicide Severity Rating Scale throughout the trial

Secondary outcome

Efficacy:

-Mean change from baseline (defined as the original baseline from the EM and CM studies) in the number of headache days of at least moderate severity during the 4-week periods after V2, V6, and V10

-Mean change from baseline (defined as the original baseline from the EM and CM studies) in the number of migraine days during the 4-week periods after V2, V6, and V10

-Proportion of participants reaching at least 50% reduction in the number of migraine days during the 4-week periods after V2, V6, and V10

-Proportion of participants reaching at least 50% reduction in the number of headache days of at least moderate severity during the 4week periods after V2, V6, and V10

-Mean change from baseline (defined as the original baseline from the EM and CM studies) in the number of days of use of any acute headache medications during the 4-week periods after V2, V6, and V10

-Mean change from baseline (day 1) in migraine-related disability score, as measured by the PedMIDAS questionnaire at V5, V8, V11, and V12

-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. 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).

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 studies and 3 Phase 3 studies in adult patients with migraine.

The pediatric migraine development program includes a completed Phase 1, single-dose, open-label study with administration of single sc doses of 75 mg in pediatric migraine patients 6 to 11 years of age, inclusive (Study TV48125-CNS-10141).

Migraine is a prevalent condition characterized by attacks of headache and associated symptoms (such as nausea, photophobia, or phonophobia).

Migraine has been classified by headache frequency in the International Classification of Headache Disorders (ICHD) 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 (Headache Classification Committee of the IHS 2013, Lipton and Silberstein 2015).

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.

Overall, authorized medications for the acute and prophylactic treatment of migraine in children and medications that are being used off-label in children have limited evidence to support their use, require ongoing patient monitoring, or are associated with undesirable or intolerable adverse effects (Barnes 2015, Kacperski 2015). Therefore, there is an unmet medical need for a safe and effective prophylactic treatment for EM and CM in the pediatric population.

The purpose of the study is to determine the long-term safety of fremanezumab.

Study objective

This study has been transitioned to CTIS with ID 2024-512837-34-00 check the CTIS register for the current data.

Main objective:
To evaluate the long-term safety and tolerability of subcutaneous test IMP in the preventive treatment of migraine in pediatric participants 6 to 17 years of age (inclusive at enrollment in the pivotal trial)

Secondary objectives:
-To evaluate the efficacy of subcutaneous test IMP in pediatric participants with migraine
-To evaluate the immunogenicity of test IMP and the impact of ADAs on clinical outcomes in pediatric participants exposed to test IMP

Study design

This is a multicenter, open-label study evaluating the long-term safety, tolerability, and efficacy of monthly sc administrations of fremanezumab for the preventive treatment of migraine (EM and CM) in male and female pediatric patients 6 to 17 years of age (inclusive at enrollment in the pivotal study).

Patients rolling over from the pharmacokinetic study (Study TV48125-CNS-10141) will begin this study at visit 1 (screening); those who are eligible will complete a 28-day baseline period before returning to the study for the first dosing at visit 2. Patients rolling over from the pivotal studies (Studies TV48125 CNS 30082 and TV48125-CNS-30083) will begin the study at visit 2. Open-label treatment will be administered sc monthly (every 28 days) for a total of 9 doses, after which the patients will be followed for 6 months from the last study drug administration for the collection of pharmacokinetic, immunogenicity samples, efficacy, and safety assessments.

Intervention

For patients who enter this study, the monthly dose of fremanezumab to be administered will be confirmed or adjusted, as appropriate, based on the

patient*s weight every 3 months. Patients weighing >=45.0 kg on the day of dosing will receive a fremanezumab dose of 225 mg. Patients weighing <45.0 kg on the day of dosing will receive fremanezumab dose of 120 mg.
For this study, monthly dosing refers to dosing approximately every 4 weeks (28 days).

Study burden and risks

Identified Risks
• injection site induration
• injection site erythema
• injection site pruritus
• injection site rash
• injection site pain
None of these risks impact the risk-benefit profile.

Important Potential Risk
Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab. 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. For additional details, refer to the current IB, Section *7.5.5.

Based on the available efficacy and safety data for fremanezumab, the benefit-risk profile is favorable.

Overall Benefit and Risk Assessment for This Study
Based on the current safety profile and the demonstrated efficacy of the sc fremanezumab dosage form as observed in adults, the overall risk and benefit assessment for this study is favorable.

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants Rolling Over from the Pivotal Efficacy Trials may be included only if they meet all of the following criteria:
a. Completion of the pivotal efficacy trial and in the opinion of the Investigator/Sponsor able to complete the trial in a safe and compliant way
b. 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. Participant may continue with a stable dose/regimen of the preventive medication they were taking during the pivotal efficacy trials
d. Willing and able to comply with trial restrictions and to remain at the clinic for the required duration during the trial period and willing to return to the clinic for the follow-up evaluation as specified in this protocol
e. Participant continues to meet appropriate criteria carried forward from the pivotal efficacy trial, as follows:
f. 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 before day 1 or are sterile
g. 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, at least 2 months before day 1)

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
h. Receipt of all recommended age-appropriate vaccines according to local standard of care and schedule
i. Good health, determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, urinalysis, and serology
j. Weight of at least 17.0 kg on the day of trial enrollment
k. BMI ranging from the 5th to 120% of the 95th percentile, incl. at day1, based on the local standard
Participants Rolling Over from Trial TV48125-CNS-10141: may be included only if they meet all of the following criteria
a. Participant is male/female, 6 - 17 years old (inclusive)
b. Written informed consent is obtained from each participant's parent or legal guardian and written assent (according to local regulations) is obtained from each participant. 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. 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. 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 of 21 out of 28 days (approximately 75% diary compliance)
d. Females who are postmenarchal or >=12 years of age may be included only if they have a negative β-HCG test before day 1 or are sterile
e. 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, at least 2 months before day 1) and for 6 months after the last dose of the 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 the IMP
f. The participant has received all recommended age-appropriate vaccines according to local standard of care and schedule
g. The participant is in good health as determined by a medical and psychiatric history, medical examination, 12-lead ECG, serum chemistry, hematology, coagulation, urinalysis, and serology
h. The participant/caregiver must be willing and able to comply with trial requirements and to remain at the clinic for the required duration during the trial period, and willing to return to the clinic for the followup evaluation
as specified in this protocol
i. Weight of at least 17.0 kg on the day of trial enrollment

j. BMI ranging from the 5th to 120% of the 95th percentile, inclusive, at screening, based on the local standard.
k. Not using preventive medications or using no more than 2 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 day 1
Participants Rolling Over from the Pivotal Efficacy Trials: Remainder of criteria applies as per the trial protocol

Exclusion criteria

Participants from the Pivotal Efficacy Trials (any criteria met):
a. Significant abnormal finding on trial entry (e.g. hematology), repeat abnormal tests for confirmation
b. Pregnant or nursing
c. Abnormal clinically significant finding on day 1 12-lead ECG
d. One of the following criteria is met:
e. Use of medications containing opioids (incl. codeine), barbiturates (incl. Fiorinal®, any other combination containing butalbital) for migraine treatment during the 3 months prior to screening visit day
f. Use of 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 1
g. Any clinically significant disease (e.g. cardiovascular), or complications of an infection
h. History of clinically significant psychiatric condition/history of a suicide attempt/history of suicidal ideation with a specific plan within the past 2 years, at the discretion of the investigator
i. Ongoing infection/known history of e.g. HIV infection/tuberculosis, Lyme disease, chronic hepatitis B or C, or a known infection of coronavirus disease 2019 (COVID-19)
j. Past or current history of cancer
k. History of hypersensitivity reactions to injected proteins, incl. mAbs, history of Stevens-Johnson Syndrome, toxic epidermal necrolysis syndrome, or the participant in concomitantly using lamotrigine
l. Current participation in another IMP/medical device trial
m. Hepatic enzymes (ALT, AST, ALP) > 1.5× ULN after a repeat test confirmation, or suspected hepatocellular damage (fulfilling Hy's law)
n. Serum creatinine > 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate (eGFR) of <75 mL/min/1.73 m2, as calculated by the revised Schwartz formula (eGFR=[0.413×Ht]/serum creatinine), or evidence of renal disease
o. Participant cannot fully participate in/successfully complete the trial for its full duration for any of the following reasons:
-In custody due to an administrative or a legal decision or in residential

treatment
-Participant/caregiver unable to be contacted in case of emergency
-Presence of any other condition, which makes the participant inappropriate for trial inclusion
-Participant is a relative of a trial center or sponsor employee who is directly involved in the trial
p. Vulnerable participants (eg, people in detention) that are vulnerable due to other conditions than age
q. Receipt of a live attenuated vaccine (eg, intranasal flu vaccine) within the 12-week period prior to day 1. Note: If a medical need arises during the trial, the participant may receive a live attenuated vaccine.
r. The participant has a known hypersensitivity to the active substance or to any of the excipients of the trial drug.
s. The participant has a current or past medical history of hemiplegic migraine.
Participants from Trial TV48125-CNS-10141 (any criteria met):
a. Use of an intervention/device for the treatment of migraine or in the head or neck area for any condition during the 2 months prior to day 1.
b. Any clinically significant disease (e.g. cardiovascular)/complications of an infection
c. Current history of clinically significant psychiatric condition/history of a suicide attempt/suicidal ideation with a specific plan within the past 2 years, at discretion of investigator
d. Ongoing infection/known history of e.g. HIV infection/tuberculosis/Lyme disease/chronic hepatitis B or C, COVID-19
e. Past or current history of cancer
f. Pregnant or nursing
g. History of hypersensitivity reactions to injected proteins, incl. mAbs/history of Stevens-Johnson Syndrome/toxic epidermal necrolysis syndrome, or participant is concomitantly using lamotrigine
h. Participation in another trial of an IMP/medical device within 30 days/ 90 days for biologics or 5 half-lives previous to screening visit day (whichever is longer) or current participation in another trial of an IMP/medical device
i. Exposure to a mAb targeting the calcitonin gene-related peptide pathway (erenumab, eptinezumab, galcanezumab, fremanezumab) during the 6 months prior to screening visit day
j. Abnormal finding on day 1 12-lead ECG considered clinically significant
k. Clinically significant abnormal finding on screening visit day, incl. hematology, blood chemistry, coagulation tests, urinalysis values/findings (repeat abnormal tests for confirmation)
l. Hepatic enzymes (ALT, AST, ALP) > 1.5× the ULN on screening visit day after confirmation in a repeat test/suspected hepatocellular damage (fulfilling Hy's law)
m. Serum creatinine > 1.5× the ULN, clinically significant proteinuria (urine dipstick +4), an estimated glomerular filtration rate (eGFR) of <75 mL/min/1.73 m2, as calculated by the revised Schwartz formula

(eGFR=[0.413×Ht]/serum creatinine), or evidence of renal disease on the day of the screening visit.
Remainder of criteria applies as per the trial protocol

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-08-2022
Enrollment:	16
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:	26-10-2020
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:	24-04-2021
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:	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:	04-12-2023
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)

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
EU-CTR	CTIS2024-512837-34-00
EudraCT	EUCTR2019-002056-16-NL
ClinicalTrials.gov	NCT04530110
CCMO	NL74048.056.20