A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache

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Primary objective:The primary objective is to assess the efficacy of LY2951742 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache. The primary outcome...

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

Summary

ID

NL-OMON46914

Source
ToetsingOnline

Brief title
I5Q-MC-CGAM

Condition

- Headaches

Synonym
chronic cluster headache, headache

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: De Sponsor van het onderzoek (Lilly)

Intervention

Keyword: CGRP neutralizing antibody, Chronic cluster headache, Galcanezumab

Outcome measures

Primary outcome

The primary endpoint will be the overall mean change from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase with LY2951742 compared with placebo.

Secondary outcome

Gated end points: See gated objectives

* Efficacy:

o Sustained response through Week 12. Sustained response is defined as a 50% or greater reduction in the weekly cluster headache attack frequency from baseline to Weeks 3/4 and maintained at Weeks 5/6, Weeks 7/8, Weeks 9/10, and Weeks 11/12.

o Mean change in the weekly cluster headache attack frequency from baseline to each 2-week interval through Week 12

o The proportion of patients with a 50% or greater reduction in the weekly cluster headache attack frequency from baseline at each 2-week interval through Week 12

o The proportion of patients with a 30% or greater reduction in the weekly cluster headache attack frequency from baseline at each 2-week interval through

Week 12

o Proportion of patients reporting a score of 1 (*very much better*) or 2

(*much better*) on the Patient Global Impression of Improvement (PGI-I) at

Month 1, Month 2, and Month 3.

* Safety and tolerability:

o spontaneously reported treatment-emergent adverse events (TEAEs)

o serious adverse events (SAEs)

o adverse events (AEs) leading to discontinuation

o suicidal ideation and behaviors assessed by solicited questioning using the

Columbia-Suicide Severity Rating Scale (C-SSRS).

* Pharmacokinetics/Pharmacodynamics (PK/PD):

o The PK of LY2951742 will be evaluated based on serum levels of LY2951742

following administration of LY2951742 and the pharmacodynamics (PD) of

LY2951742 will be evaluated based on plasma concentrations of CGRP prior to and

following LY2951742 administration

Study description

Background summary

Cluster headache is a rare but disabling primary headache disorder characterized by episodic attacks of intense unilateral headache and the frequent association of autonomic symptoms such as lacrimation, conjunctival injection, and nasal congestion. There are significant unmet needs for just about every clinical aspect of the patient with cluster headache, particularly related to the severity of the disease and treatment options. The majority of

patients experiencing cluster headache attacks rate their pain intensity as near to or at the worst pain imaginable. Increased plasma or serum levels of calcitonin gene-related peptide (CGRP) have been associated with painful syndromes such as migraine and cluster headache. LY2951742 is a humanized monoclonal antibody that binds to and neutralizes CGRP. LY2951742 has been identified for clinical development in pain conditions relevant to the CGRP pathway such as migraine, and, in completed studies to date, LY2951742 was shown to alter plasma CGRP concentrations, which is consistent with the binding of the antibody (LY2951742) to CGRP. The similarities between migraine and cluster headache, the role of CGRP in both disorders and the clinical efficacy observed with LY2951742 to date for the preventive treatment of migraine support the evaluation of the CGRP neutralizing antibody LY2951742 for the treatment of cluster headache.

Study objective

Primary objective:
The primary objective is to assess the efficacy of LY2951742 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache. The primary outcome measure will be the weekly cluster headache attack frequency. The primary endpoint is the overall mean change from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase with LY2951742 compared with placebo.

Main secondary:
Gated objectives:
* To assess the efficacy of LY2951742 300 mg compared with placebo in the estimated mean proportion of patients with a 50% or greater reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase.

* To assess the efficacy of LY2951742 300 mg compared with placebo in the proportion of patients meeting sustained response through Week 12. For this analysis, sustained response is defined as a 50% or greater reduction in the weekly cluster headache attack frequency from baseline to Weeks 3/4 and maintained at Weeks 5/6, Weeks 7/8, Weeks 9/10, and Weeks 11/12.

Other secondary objectives:
* To assess whether LY2951742 is superior to placebo considered certain end points (see section *end points*.
* To compare LY2951742 300 mg with placebo on safety and tolerability measures
* To assess the development and consequences of anti-drug antibodies (ADA) to LY2951742 in patients exposed to LY2951742; to provide samples for subsequent evaluation of neutralizing ADA (NAb).
* To evaluate the pharmacokinetics of LY2951742.

Tertiary/exploratory objectives:
To assess whether LY2951742 is superior to placebo as measured by:
* Proportion of patients randomized to LY2951742 meeting *very much better* or *much better* on the PGI-I at Month 9 and Month 15.
* Mean change in the weekly number of times of abortive medication use from baseline to each 2-week interval through Week 12 comparing LY2951742 with placeboChange in percentage of times of using acetaminophen/paracetamol or NSAIDs from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
* Change in percentage of times using oxygen from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo.
* Change in percentage of times using triptan from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo
* Change in percentage of times of using acetaminophen/paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) from baseline for each 2-week interval through Week 12 comparing LY2951742 with placebo
* Responder analyses of LY2951742 compared with placebo from baseline to each 2-week interval through Week 12 for the proportion of patients meeting:
o a 75% or greater reduction in the weekly cluster headache attack frequency
o a 100% reduction in weekly cluster headache attack frequency
* Mean change from baseline to each 2-week interval through Week 12 in the cluster headache attack average weekly pain severity based on 5-point pain severity scale comparing LY2951742 with placebo.
* To assess target engagement by LY2951742 via measurements of plasma CGRP concentrations
* To examine the relationship between baseline plasma CGRP levels and the primary and secondary efficacy endpoints.

Study design

Study CGAM is a Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg for the prevention of chronic cluster headache. The study has 5 study phases (SP):
* SP I (screening/washout phase): 0-65 days
* SP II (pre-randomization diary phase): approximately 2 weeks
* SP III (double-blind treatment phase): 12 weeks
* SP IV (optional open-label extension phase): approximately 52 weeks
* SP V (post-treatment follow-up phase): 16 weeks
Section 7.1 of the Clinical Protocol gives a detailed description of the study design.

Intervention

This study includes 2 treatment groups: placebo or LY2951742 300 mg (1:1). Each treatment group will be administered three 1 ml SC injections, by qualified site personnel, every 30 days for a total of 2 administrations during SP III.

The designated unblinded site personnel responsible for preparing LY2951742 and placebo doses should refer to the Pharmacy Binder Dosing Instructions for LY2951742 Drug Product, 75 mg, for the preparation and dosing instructions for both LY2951742 and placebo.
A patient number will be assigned to each patient after the ICF is signed and dated. Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS system will be programed following the dynamic allocation (minimization) method of Pocock and Simon (1975) to balance the treatment arms for the factors of gender, average daily attack frequency (*4 attacks per day, >4 attacks per day), verapamil (yes/no) and investigative site.

Study burden and risks

The study drug is accompanied by certain risks.
Events seen most frequently (*10%) in patients with migraine and cluster headache who received LY2951742 are pain, redness, itching, bruising of skin, swelling, and/or hardening at the site of injection.

The study procedures, including blood draws, ECGs, subcutaneous injections and urine analysis, also have certain risks. The study drug, the study procedures and the combination may also have other, unknown risks.

Please refer to the subject information sheet and the Investigator*s Brochure for a detailed description of the risks.

Contacts

Public
Eli Lilly

Island House, Eastgate Business Park -
Little Island -
IE
Scientific
Eli Lilly

Island House, Eastgate Business Park -
Little Island -
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male and female outpatients 18 to 65 years of age inclusive prior to signing informed consent.
2. At Visit 1, patients must have a history of chronic cluster headache and distinguished from episodic cluster headache as defined by IHS ICHD-3 beta (ICHD-3 2013).
3. Not to be shared with potential patients: During SP II, have a baseline cluster headache attack frequency (based on ePRO vendor eligibility report) of:
[3a] minimum of 8 cluster headache attacks
[3b] maximum of 8 cluster headache attacks per day
Note: a patient with 2 or more consecutive days without an attack during the baseline assessment will be excluded. If a patient fails eligibility due to the occurrence of >8 cluster headache attacks per day, the patient may be considered for rescreen.
4. For patients on preventive treatment for cluster headache, must be on a stable regimen (with stable dose for at least 2 months prior to the start of SP II), which may include verapamil (maximum daily dosage: 480 mg), lithium, melatonin, valproate, gabapentin, and topiramate. Use of any other preventive treatments for cluster headache is not allowed.
5. In the opinion of the investigator, spontaneous remission during the doubleblind treatment phase is not anticipated based on the patient*s history of cluster periodicity.
6. At Visit 1, are able to distinguish cluster headache attacks from other headaches (i.e. tension-type headaches, migraine).
7. Investigator judges the patient as reliable to follow all study procedures, keep all study visits, and be compliant with study requirements.
8. Women of child-bearing potential may participate in the study.
a. Women of child-bearing potential must test negative for pregnancy (based on a serum pregnancy test) at the time of enrollment and must agree to use a reliable method of birth control during the study and for 5 months following the last dose of investigational product.
b. Male patients agree to use a reliable method of birth control during the study and for 5 months following last dose of investigational product.
c. Women not of child-bearing potential are those who are infertile due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy with or without

hysterectomy or at least 6 weeks after tubal ligation) confirmed by medical history, or menopause.
9. Have not taken any of the following excluded medications or other treatments for cluster headache within the time frame noted:
a. use within 14 days prior to SP II of any of the following: dihydroergotamine or ergot derivatives; gabapentin; lithium; melatonin; methergine; topiramate; valproate; verapamil, opioids
b. use within 30 days prior to SP II of any of the following: systemic or injected corticosteroids; occipital nerve block; any ot her cranial or extracranial nerve block; any neurostimulation treatment.
Note: Patients are allowed to use only the following for acute/abortive treatment for their cluster headache attacks: high-flow oxygen; oral triptans, sumatriptan subcutaneous injection; sumatriptan nasal spray; zolmitriptan nasal spray; acetaminophen and NSAIDs.
10. Throughout the study (Informed Consent through Visit 24), agree to refrain from the use of drugs of abuse per United States Federal Guidelines such as, but not limited to, cannabinoids, cannabis, psilocybin (mushrooms), LSD and 2-bromo-LSD.
11. Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (for example, Facebook, Twitter, LinkedIn, Google+, etc.) until the entire trial has completed.
12. Have given written informed consent.
The planned patient population includes adult outpatients (18 to 65 years of age inclusive) who meet the International Headache Society*s International Classification of Headache Disorders, Third Edition, beta version (IHS ICHD-3-beta), diagnostic criteria for Chronic Cluster Headache. Please refer to Clinical Protocol page 30 for ICHD-3 beta diagnostic criteria for Cluster Headache.

Exclusion criteria

13. Current enrollment in, or discontinuation within the last 30 days prior to Visit 1 from, a clinical trial involving any investigational drug or device, or concurrent enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
14. Current use or any prior exposure to any CGRP antibody (including LY2951742), any antibody to the CGRP receptor, or antibody to nerve growth factor (NGF) including past participation in a clinical trial investigating CGRP, CGRP receptor, or NGF antibodies.
15. Patients who are taking other therapeutic antibodies or are expected to take during the course of the study (for example, adalimumab, infliximab, trastuzumab, bevacizumab, etc.). Prior use of other therapeutic antibodies is allowed if an adequate wash-out has occurred (*5 half-lives) prior to SP II.
16. Any of the following headache-related or pain-related conditions are exclusionary:
a. Current diagnosis of Medication Overuse Headache as defined by ICHD-3 beta within 3 months prior to Visit 3. Note: daily triptan use for daily cluster headache attacks is allowed provided it is not resulting in an MOH of some other headache type.
b. Lifetime history of migraine variants that could implicate or could be confused with ischemia; specifically, hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine,

and basilar-type migraine defined by ICHD-3 beta.
c. Are taking indomethacin and/or are suspected of having another distinct trigeminal autonomic cephalalgia such as hemicrania continua, paroxysmal hemicrania, or shortlasting unilateral neuralgiform headache attacks (SUNCT or SUNA).
d. Have other significant pain problem that might confound the study assessments in the opinion of the investigator.
17. Patients who have taken botulinum toxin type A or B, that was administered in the head or neck area, within 4 months of SP II for treatment of cluster headache or other disorders, or for cosmetic use.
18. Any (lifetime) history of deep brain stimulation.
19. Evidence of significant active or unstable psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders.
Note: Patients with major depressive disorder or generalized anxiety disorder, whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medication(s).
20. Are considered by the investigator to be at significant risk for suicide.
21. Women who are pregnant or nursing.
22. Any of the following cardiovascular-related conditions are exclusionary:
a. Prior to Visit 3 (randomization), have ECGs showing acute abnormalities of:
i. evidence of delayed ventricular repolarization including but not limited to a corrected QT (Bazett*s QT interval [QTcB]) interval >470 msec for women an >450 for men, and/or
ii. ii. evidence of atrioventricular (AV) depolarization of PR>220, or conduction delay of QRS>120, and/or
iii. iii. evidence of ischemia or any of the qualitative findings indicative of ST or J-point elevation, excluding those findings consistent with early repolarization (nonischemic).
b. History of myocardial infarction (MI), unstable angina (UA), percutaneous coronary intervention, coronary artery bypass graft, or deep vein thrombosis/pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty.
c. Any lifetime history of vasospastic angina or stroke, or recent history (6 months) of emergency room visit for chest pain in which an ischemic or cardiac event was not ruled out.
d. Clinical evidence of peripheral vascular disease (e.g., Buerger*s Disease) or a diagnosis of Raynaud*s Phenomenon.
e. Have any history of intracranial or carotid aneurysm, intracranial hemorrhage, or stroke.
f. Have uncontrolled high blood pressure, characterized by systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg on 2 or more blood pressure assessments prior to Visit 3.
23. Any of the following medical conditions are exclusionary:
a. Have a lifetime history of seizures (except for childhood febrile seizures).
b. Have a history or presence of any other medical illness including but not limited to any cardiovascular, hepatic, respiratory, hematological, endocrine, psychiatric or neurological disease, or any clinically significant laboratory abnormality, that in the judgment of the investigator, indicates a medical problem that would preclude study participation.
c. Prior to Visit 3, patients with an elevation of *2X the upper limit of normal (ULN) for alanine aminotransferase (ALT), or *1.5X ULN for total bilirubin (TBL) or alkaline phosphatase (ALP)

may be retested. The patient*s results must be discussed and judged not clinically significant by Lilly Medical prior to enrollment.
d. Patients with a history of an intracranial tumor or head trauma must be discussed and judged not to indicate a medical problem that would preclude study participation by Lilly Medical prior to enrollment.
24. Any of the following drug- or alcohol- related conditions are exclusionary:
a. Patients who do not agree to abstain from alcohol consumption during SP II and SP III of the study. However, patients are encouraged to abstain from alcohol consumption throughout the entire study.
b. History of drug, alcohol, opioid, or barbiturate abuse/de pendence within 1 year prior to SP II (excessive or habitual use as judged by the Investigator), or currently using drugs of abuse (including, but not limited to opioids, barbiturates and cannabis), or any prescribed or over-the-counter medication in a manner that the Investigator considers indicative of abuse/dependence. This exclusion criterion does not apply to tobacco and caffeine.
c. History of use of psilocybin (mushrooms), LSD, or 2-bromo-LSD within 2 months prior to SP II.
d. Have a positive urine drug screen (UDS) for any substances of abuse prior to randomization. Note: One retest may be performed if the UDS is positive for any prescribed substance or if, in the judgment of the investigator, there is an acceptable explanation for the positive result. The results of the retest must be negative at or prior to Visit 3. If a patient fails eligibility due to a positive UDS, the patient may be considered for rescreen.
25. Completion of less than 5 of 7 days of the daily ePRO diary entries during the baseline assessment (defined in Statistical Methods, Section 12) as evidence of inadequate compliance.
26. Employees of Lilly or investigational site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
27. Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to LY2951742 or to any of the inactive ingredients.
28. Patients with a body mass index (BMI) *40 kg/m2.

Study design

Design

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

Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2017
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Galcanezumab
Generic name:	LY2951742

Ethics review

Approved WMO Date:	22-08-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-09-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-02-2017
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-01-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2014□005429□11-NL
ClinicalTrials.gov	NCT02438826
CCMO	NL58464.028.16