A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache

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Primary: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 episodic cluster headache. The primary outcome measure will...

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

Summary

ID

NL-OMON45305

Source
ToetsingOnline

Brief title
I5Q-MC-CGAL

Condition

- Headaches

Synonym
Episodic 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, Episodic cluster headache, Galcanezumab

Outcome measures

Primary outcome

The primary endpoint will be mean change in weekly cluster headache attack frequency from baseline to Week 3 with LY2951742 compared with placebo.

Secondary outcome

Gated objective: Response is defined as a reduction from baseline of 50% or greater in the weekly cluster headache attack frequency.

Efficacy:

o The proportion of patients with a 50% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8

o The proportion of patients with a 30% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8

o Mean change in the weekly cluster headache attack frequency from baseline for each weekly interval through Week 8

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 Week 4 and Week 8.

Safety and tolerability:

o spontaneously reported treatment-emergent adverse events (TEAEs)

o serious adverse events (SAEs)

o discontinuation rates

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:
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 episodic cluster headache. The primary outcome measure will be the weekly cluster headache attack frequency.

Main secondary objective:
Gated objective: To assess the efficacy of LY2951742 compared with placebo in the proportion of patients meeting response at Week 3.

Other secondary objectives:
• To assess whether LY2951742 is superior to placebo considered certain end points (see section *end points*.
• To compare the safety and tolerability of LY2951742 with placebo in patients with episodic cluster headache
• 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 ADAs (NABs) upon availability of the validated assay.
• To evaluate the pharmacokinetics of LY2951742.

Tertiary/exploratory objectives:
To assess whether LY2951742 is superior to placebo as measured by:
• Mean change in the weekly number of times an abortive medication was taken from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
• Change in percentage of times using oxygen or triptan from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
• Change in percentage of times of using acetaminophen/paracetamol or NSAIDs from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
• The proportion of patients with a 75% or greater reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
• The proportion of patients with a 100% reduction in the weekly number of cluster headache attacks from baseline for each weekly interval through Week 8 comparing LY2951742 with placebo.
• Mean change in the cluster headache attack average weekly pain severity (based on 5-point scale) from baseline through Week 8 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 CGAL is a Phase 3 multi-center, outpatient, randomized, double-blind, placebo-controlled study of LY2951742 300 mg in the prevention of episodic cluster headache. The study has 4 study phases (SP): SP I (screening/washout), SP II (pre-randomization diary), SP III (randomized, double-blind, placebo-controlled treatment), and SP IV (post-treatment follow-up). Patients who discontinue the study during the double-blind treatment phase should enter the post-treatment follow-up phase. The proposed duration of the double-blind treatment phase is 8 weeks, with the primary endpoint assessed during Week 3 after the first IP dose.
Section 7.1 of the Clinical Protocol gives a detailed description of all study phases and the patient flow through SP I and SP II.

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) and investigative site.

Study burden and risks

The study drug is accompanied by certain risks.
Events seen most frequently (>=2%) in patients with migraine who received LY2951742 and at a rate greater than for those on placebo (data from 380 people) are pain at the site of injection, an infection of your upper breathing system, such as bronchitis, cold, or cold-like symptoms, head cold, back pain, painful menstruation and tooth ache.
Events seen most frequently (>=2%) in a study of people with mild to moderate knee pain due to a type of arthritis in patients who received LY2951742 and at a rate greater than those on placebo (data from 151 people) are the flu and

headache.
The study procedures, including blood draws, 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

Papendorpseweg 83
Utrecht 3528 BJ
NL
Scientific
Eli Lilly

Papendorpseweg 83
Utrecht 3528 BJ
NL

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 episodic cluster headache and distinguished from chronic cluster headache as defined by IHS ICHD-3 beta (ICHD-3 2013).

3. At Visit 1, have a prior history of a cluster period lasting 6 weeks or greater.
4. At Visit 1, for patients currently in an active cluster period:
a. In opinion of investigator, would be expected to continue in the current period for at least another 6 weeks based on previous cluster period history.
b. They are not taking any excluded medications that require washout (see Criteria #9)
Note: patients not meeting criteria a and b must be a screen fail, but they may be considered for re-screening
5. Not to be shared with potential patients: During SP II, have a baseline weekly cluster headache attack frequency (based on ePRO vendor eligibility report) preceding Visit 3 of:
a. minimum of 1 cluster headache attack every other day and at least 4 total attacks
b. 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 during their current cluster headache period, if, in the opinion of the investigator, the patient would be expected to continue in the current period for at least another 6 weeks based on previous cluster period history. If the patient is not expected to continue in the current period for another 6 weeks, the patient may be considered for rescreen during their next cluster headache period.
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 9), agree to refrain from the use of drugs of abuse per United States Federal Guidelines (Schedule I) 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 Episodic Cluster Headache. Please refer to Clinical Protocol page 27 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.
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/dependence 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 during their current cluster headache period, if, in the opinion of the investigator, the patient would be expected to continue in the current period for at least another 6 weeks based on previous cluster period history. If the patient is not expected to continue in the current period for another 6 weeks, the patient may be considered for rescreen during their next cluster headache period.
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):	04-01-2017
Enrollment:	18
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:	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:	05-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-05-2018
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	EUCTR2015-000149-22-NL

Register	ID
ClinicalTrials.gov	NCT02397473
CCMO	NL58463.028.16