A Phase 2, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Ulcerative Colitis

Published: 12-11-2015
Last updated: 19-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON46940

Source
ToetsingOnline

Brief title
AMAC

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflamatory bowel disease, Ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly and Company
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Ulcerative Colitis

Outcome measures

Primary outcome

The primary efficacy endpoint is the clinical remission at Week 12

Secondary outcome

Secondary efficacy endpoints are clinical response at Week 12 and endoscopic

remission at Week 12 and Week 52

Study description

Background summary

Ulcerative colitis (UC) is a chronic disease of unknown cause that is characterized by inflammation in the colon. Subjects have intermittent disease flares interspersed with periods of remission; the primary symptoms are blood in the stool, diarrhea, and abdominal pain, which reduce overall quality of life. Many subjects with UC experience a severe clinical course: approximately 30% require colectomy within 10 years of diagnosis.

Various biologic therapies that target specific immunological pathways have been studied as potential therapeutics for UC. Experimental studies suggest that blocking the interleukin-23 (IL-23)/T helper 17/interleukin-17 immune axis alone is effective to treat inflammation in UC. Agents specifically targeting the IL-23 p19 subunit, including LY3074828, are in development for many autoinflammatory diseases to determine whether improvement in efficacy can be achieved by targeting IL-23 specifically. LY3074828 is a humanized immunoglobulin G4-variant monoclonal antibody (molecular weight approximately 144,000 Da) that is directed against the p19 subunit of IL-23 and does not bind interleukin-12.

Eli Lilly has an ongoing (database locked, clinical study report pending) Phase

1 (first-in-human) ascending-dose study in which 33 subjects with psoriasis and 5 healthy subjects have each been administered a single dose of LY3074828. No serious adverse events were reported, and no
subject discontinued because of an adverse event (AE).

This Phase 2 study will provide efficacy data on intravenous (IV) administration of LY3074828 (3 doses versus placebo) in subjects with moderate to severe UC.

Study objective

The primary objective of this study is to test the hypothesis that treatment with LY3074828 is superior to placebo in inducing clinical remission at Week 12 in subjects with moderate to severe ulcerative colitis (UC).

The secondary objectives are:
-To evaluate the safety and tolerability of treatment with LY3074828
-To evaluate the efficacy of treatment with LY3074828 in inducing a clinical response at Week 12
-To evaluate endoscopic remission at Week 12 and Week 52
-To evaluate the effect of maintenance treatment with LY3074828 on the durability of clinical remission,
endoscopic remission, and clinical response at Week 52
-To evaluate the effect of LY3074828 on health outcomes/quality of life measures (Inflammatory Bowel Disease Questionnaire score, 36-Item Short Form Health Survey score, and Patient*s Global Impressions of Severity score, and Patient*s Global Impressions of Improvement score)
-To characterize the pharmacokinetic (PK) profile of LY3074828

Study design

Study I6T-MC-AMAC is a multicenter, randomized, double-blind, parallel-arm, placebocontrolled trial in which approximately 240 subjects will be randomized. Subjects must have moderate or severe UC (defined as a Mayo score of 6 to 12 with an endoscopic subscore >=2). Approximately two-thirds (~160) of the subjects randomized to study treatment must have been exposed to at least 1 previous biologic therapy (tumor necrosis factor [TNF] antagonist or vedolizumab), and approximately one-third (~80) of the subjects will be naive to biologic therapy.

Screening Period: Subjects will be evaluated for study eligibility <=28 days before the baseline visit. At the baseline visit, subjects who fulfill the eligibility criteria will be randomized equally to 1 of 4 induction treatment arms.

Induction Period: A 12-week induction period is designed to establish the

efficacy and safety of LY3074828 administered IV at Weeks 0, 4, and 8. Subjects will be stratified across the treatment arms on the basis of previous exposure to biologic therapy for treatment of UC.

Maintenance Period: The maintenance period is designed to explore the safety and durability of clinical responses and remissions to treatment with 200-mg LY3074828 administered subcutaneously (SC) every 4 weeks (Q4W) or every 12 weeks (Q12W). Subjects defined as having clinical responses at Week 12 will continue study participation in the maintenance period up to Week 104. Subjects who do not meet clinical response criteria at Week 12 will have the option to continue in a study Extension Period or discontinue from the study. Responding subjects who have received LY3074828 in the induction period will be re-randomized to 1 of 2 LY3074828 maintenance treatment arms (200 mg Q4W or 200 mg Q12W); these subjects will be stratified according to their Week-12 remission status. Any responding subjects in the placebo arm SC Q4W will remain on placebo. After Week 52, subjects who experience worsening of UC (partial Mayo score of 7 or more) may receive rescue treatment with LY3074828 200 mg SC Q4W.
Maintenance Follow-Up Period: The follow-up period will include a visit every 4 weeks for a total of 16 weeks following Week 104 to assess subject safety.

Extension Period: Subjects who complete the study induction period (through Visit 7) but do not have a clinical response may choose to participate in the unblinded study extension period following consultation with, and at the discretion of, the investigator.
Extension Follow-Up Period: A follow-up period will include a visit every 4 weeks for a total of 16 weeks following Extension Week 92 to assess subject safety.

Intervention

Induction Period:
50 mg, 200 mg, or 600 mg LY3074828 given as an IV infusion (Weeks 0, 4, 8)

The 50-mg and 200-mg arms will use exposure-based dosing: doses for individuals in the 50-mg and 200-mg arms may be increased at Weeks 4 and 8 if the projected trough concentrations of LY3074828 for those visits fall below prespecified thresholds. Dose level changes in these patients will be communicated to the site by the sponsor. Doses administered to any individual will not exceed 600mg.

Maintenance Period:
Responding subjects (as defined by the protocol) will be randomized to receive 200 mg LY3074828 given SC either Q4W or Q12W

Extension Period:
Nonresponding subjects (as defined by the protocol) may continue in the study

and receive LY3074828.

Study burden and risks

Blood Tests
You may feel an uncomfortable needle prick when your blood is drawn. There may be side effects of having blood draws such as:
• Feeling faint
• Bruising
• Bleeding
If you feel faint, tell the study doctor or staff right away.

Chest X-rays
X-rays are a form of radiation*like light or radio waves*that can be directed at the body. The part of your body to be X-rayed is placed against a flat surface while a camera-like machine is placed on the opposite side of the body. This machine sends out a very small burst of radiation which passes through the body to create images of the body. The amount of radiation from one X-ray is similar to the normal amount a person receives in ten days from our natural surroundings, thus, the risk from an X-ray is minimal.

ECG
The ECG (electrocardiogram) is a recording of the electrical action of the heart. During this procedure, you will need to lie still for a few minutes so recording electrodes can be placed on your chest. The electrodes may cause some discomfort when they are put on and taken off your skin. If you are a male and have chest hair, it may need to be shaved off on the areas where the electrodes will be placed.

Infusions
For most people, IV infusions (infusions in a vein) do not cause any serious problems. However, sometimes problems may happen. IV infusions may cause bleeding or bruising. They may cause infections and/or pain at the needle site. The IV in your vein is put in with equipment that is sterile (germ-free) but germs from your skin may get to your vein from the skin around the needle, and may cause swelling, redness, and fever. Phlebitis is inflammation of a vein. If you have phlebitis, you may feel swelling, pain, and redness around the vein. Rarely, a blood clot or an air bubble can get into the vein from an IV infusion, and can block blood flow. This is called embolism; there is a low risk of this. Extravasation is another problem that can happen. This is when some of the fluid being infused is accidentally leaks into the surrounding flesh instead of into the vein.

Injections
For most people, injections do not cause any serious problems. Sometimes they may cause bleeding or bruising where the injection is given. Sometimes, people may have discomfort and/or pain at the site of the injection. Rarely,

injections cause infections. Additionally, if a needle is placed in a blood vessel (IV infusion), the risk of infection could include germs entering into the blood system, which can be serious; there is a low risk of this. Injections in this study will be given either by IV infusion or just under the skin, in the area of the abdomen or thigh.

Endoscopy & Intestinal Biopsy
To see how your ulcerative colitis is doing, your rectum and large bowel will be examined by endoscopy (flexible sigmoidoscopy or colonoscopy). In order to get accurate results, the rectum and the lower colon must be completely empty of stool. Your doctor will give you detailed instructions on preparation for the procedure. Sedatives are usually given in your vein prior to the procedure, so that you become sleepy and relaxed, and to reduce pain.

Endoscopy is performed with an endoscope; a flexible, tube-like instrument that takes pictures of the lining of the colon. The instrument is inserted gently into the anus and advanced slowly into the rectum and the colon by the doctor. The video images (pictures) of the rectum and colon are recorded and saved to a computer by your study team. The saved images are downloaded to a secure/confidential website. The images are reviewed by a doctor who is an expert in looking at endoscopy pictures. Video images do not show your name; they have a study identification number and your subject identification number. There is a small chance that the video images may accidentally identify you, however that is not planned or expected. In addition, tissue samples (biopsies) are taken from the bowel during the endoscopy procedure by your doctor. The biopsies are about the size of a pencil-tip, and up to 10 biopsies will be taken at each endoscopy procedure. Persistent bleeding after biopsy or polyp removal (if needed) can occur. Biopsy results can be used to see how your disease is doing, and can identify a cancer of the intestine (bowel) that you did not know about.

Complications of endoscopy are rare and usually minor. As mentioned above, bleeding may occur at the site of biopsy or polyp removal, but the bleeding is usually minor and self-limited, or can be reduced using the endoscope during the procedure. An even less common complication is a perforation (tear) in the colon, but these perforations usually do not require surgery. Other potential complications include: reactions to the sedatives used or local irritation to the vein where medications were injected. Please immediately tell the study doctor or study staff if you have any of these symptoms, or any other side effects, during the study.

Other Risks
In addition to the risks named above, LY3074828 and the study procedures may have other unknown risks.
There may be unknown risks of possible harmful interaction with other medication you may be taking.
At any time during this study, you may experience a return or worsening of your

disease. It may be more likely that you will experience such return or worsening of your disease if you receive placebo as your study drug.

There may also be unknown risks to an embryo, fetus, or nursing infant.

Contacts

Public
Eli Lilly and Company

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

This study will include male or female subjects >=18 and <=75 years of age with moderate to severe active UC (defined as a Mayo score of 6 to 12 with an endoscopic subscore >=2).

Exclusion criteria

This study will include male or female subjects >=18 and <=75 years of age with moderate to severe active UC (defined as a Mayo score of 6 to 12 with an endoscopic subscore >=2).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-06-2016
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	mirikizumab
Generic name:	LY3074828

Ethics review

Approved WMO

Date:	12-11-2015
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2019
Application type:	Amendment

Review commission: METC Amsterdam UMC

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	EUCTR2015-003123-57-NL
ClinicalTrials.gov	NCT02589665
CCMO	NL55331.018.15

Study results

Date completed: 31-01-2019

Actual enrolment: 7

Summary results
Trial is onging in other countries