A randomized, double-blind, placebo and positive controlled, parallel group study to investigate the QTc exposure response, pharmacokinetics, safetyand tolerability after multiple therapeutic and supratherapeutic dosing of etrasimod (APD334) in healthy adult subjects

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

Summary

ID

NL-OMON44472

Source
ToetsingOnline

Brief title
APD334 QTc, safety and PK study

Condition

- Autoimmune disorders

Synonym
autoimmune diseases

Research involving
Human

Sponsors and support

Primary sponsor: Arena Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: APD334, PK, QTc

Outcome measures

Primary outcome

Change-from-baseline QTc (ΔQTc) with the selected primary correction method.

Secondary outcome

Change-from-baseline HR (ΔHR), QTc with the correction methods not selected as

primary, PR, QRS, RR, and QT; Placebocorrected

change-from-baseline HR, QTcF, QTcS, QTcI, QTcP, PR, QRS,RR, and QT;

Categorical outliers for QTc, HR, PR, and QRS; Frequency of T-wave

morphology and U-wave presence changes.

Study description

Background summary

Etrasimod is a new investigational compound that may eventually be used for the treatment of autoimmune diseases such as ulcerative colitis, an inflammatory disease of the colon or skin diseases such as psoriasis or pyoderma gangrenosum.

Etrasimod is able to bind to a specific protein on the cell surface of lymphocytes (a kind of white blood cell). This specific protein is called S1P

receptor. Lymphocytes are involved in the inflammatory processes of autoimmune diseases including ulcerative colitis, pyoderma gangrenosum or psoriasis. By binding to this S1P receptor, etrasimod prevents lymphocytes from reaching sites of inflammation. It is believed that this will help to treat different inflammatory diseases.

Moxifloxacin (Avalox) is used as a control during this study. Moxifloxacin is on the market as an antibiotic and has been available in the European Union for almost 10 years. The volunteer will receive a patient information leaflet for more information on this compound.

Study objective

The purpose of the study is to investigate the effect of etrasimod on the values of specific ECG parameters. Importantly, the study will assess whether there is a prolongation of the QT interval following etrasimod treatment. When the QT interval is prolonged, repolarization (return to resting state) of the heart is delayed. This means that cardiac (heart) cells need more time to prepare for the next beat. When a new heartbeat is about to start and not all cardiac cells are ready for repolarization, arrhythmias could develop. For this study the expected small changes to your ECG recordings are considered to be relatively safe.

It will also be investigated to what extent etrasimod is safe, tolerated, and how quickly and to what extent etrasimod is absorbed and eliminated from the body (this is called pharmacokinetics).

Study design

The actual study will consist of a period during which you will stay in the clinical research center in Groningen (location Martini Hospital) for 18 days (17 nights).

During the study, the volunteer will receive etrasimod, moxifloxacin or placebo after an overnight fast (at least 10 hours no eating and drinking) as a tablet (etrasimod and etrasimod-matching placebo) and/or as a capsule (moxifloxacin and moxifloxacin-matching placebo) with 240 milliliters of (tap) water.

Intervention

The study will consist of a period of approximately 2 * weeks during which the volunteer will receive either multiple oral doses of etrasimod for 14 days (Treatment A) or a single dose of moxifloxacin either on Day 1 (Treatment B1) or on Day 15 (Treatment B2). In all treatments (Treatments A, B1 and B2), subjects will receive placebo matching etrasimod and/or placebo matching moxifloxacin from Day -1 to Day 15.

Whether the volunteer will receive Treatment A, Treatment B1 or Treatment B2 will be determined by chance. In each group, 50% of the volunteers will receive Treatment A and 50% will receive Treatment B (this could be either Treatment B1 or Treatment B2).

Treatment A Treatment B
(30 subjects)
Treatment B1 TreatmentB2
Day (15 subjects) (15 subjects)

Day -1 Placebo E once Placebo E once Placebo E once
Day 1 2 mg etrasimod and Placebo M once 400 mg Moxifloxacin and Placebo E once Placebo E and Placebo M once
Days 2-7 2 mg etrasimod once daily Placebo E once daily Placebo E once daily
Days 8-12 3 mg etrasimod once daily Placebo E once daily Placebo E once daily
Days 13-14 4 mg etrasimod once daily*) Placebo E once daily Placebo E once daily
Day 15 Placebo M once Placebo M once 400 mg Moxifloxacin once

*) Depending on the results of the previous dose level, it may be decided to continue with the 3 mg dose level instead of increasing to the 4 mg dose level
Placebo E = etrasimod-matching placebo
Placebo M = moxifloxacin-matching placebo

Study burden and risks

All potential drugs cause adverse effects; the extent to which this occurs differs.

ETRASIMOD
To date at least 80 people have taken etrasimod. Because of this, only limited information is available regarding side effects in humans. Etrasimod has been administered so far to 30 healthy volunteers in single doses up to 5 mg and to 50 healthy volunteers in repeat doses up to 3 mg daily for up to 21 days. To date there is no information about the effects, either good or bad, of etrasimod over longer periods. There are other studies ongoing in other disease (ulcerative colitis), but the safety data from those studies are not yet available.

Reported side effects of the study compound:
The following side effects have been observed in healthy subjects taking etrasimod in completed studies at frequency more than 5% and at frequency higher than placebo:
• Constipation - 6% (or 6 out of 100 patients)
• Diarrhea - 9% (or 9 out of 100 patients)

Other possible side effects of the study compound:
• Temporary reduction in the number of lymphocytes (type of white blood cells), called lymphopenia, is expected due to the way of action of the study compound. Lymphocytes are part of the immune system which defends the body against the diseases including bacterial and viral infections. In all subjects who took etrasimod so far, the number of lymphocytes returned to normal after etrasimod was discontinued.

• Delayed travel of electrical pulses in the heart. In prior studies with etrasimod delayed travel of electrical pulses in the heart was observed in 5 subjects (5 cases grade 1 AV block). One of those subject also experienced intermittent stop in the travel of the electrical pulse (grade 2 AV block). The severity in all these reactions was mild and no treatment was necessary.

FINGOLIMOD
Side effects reported with the use of another similar drug, called *Gilenya®* (Fingolimod), which is a drug from the same group as the study compound, could occur. Please note that patients with Multiple Sclerosis that reported some of the following side effects have been using Gilenya for an extended period. Please note as well that Fingolimod will not be used in this study.

Common (may affect up to 1 in 10 people):
• Lung disorders
• Herpes virus infection (shingles or herpes zoster)
• Bradycardia (slow heart rate), bradyarrhythmia
• Basal cell carcinoma (BCC) (a kind of skin cancer)
Uncommon (may affect up to 1 in 100 people):
• Pneumonia (with symptoms such as fever, cough, difficulty breathing)
• Macular edema (with symptoms such as shadows or blind spot in the center of the vision, blurred vision, problems seeing colors or details)
• Reduction in blood platelets which increases risk of bleeding or bruising
Rare (may affect up to 1 in 1,000 people):
• Posterior reversible encephalopathy syndrome (PRES). Symptoms may include sudden onset of severe headache, confusion, seizures and/or vision disturbances.
• Lymphoma
Very rare (may affect up to 1 in 10,000 people):
• Electrocardiogram anomaly (T-wave inversion)
Isolated cases (frequency cannot be estimated from the available data):
• Cryptococcal infections (a type of fungus infection), including cryptococcal meningitis with symptoms such as headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion
Not known (frequency cannot be estimated from the available data):
• Allergic reactions, including symptoms of rash or itchy hives, swelling of lips, tongue or face, which are more likely to occur on the day of the start with treatment
• Progressive multifocal leukoencephalopathy (PML)

The following other side effects that were also reported by using Fingolimod:

Very common adverse events (may affect more than 1 in 10 people):
Infection from flu virus with symptoms (such as tiredness, chills, sore throat, aching in the joints or muscles, fever), sinusitis, headache, diarrhea, back pain, elevated liver enzymes, and cough.

Common (may affect up to 1 in 10 people):
Tinea versicolor (ringworm), dizziness, migraine, low level leucocytes (a type of white blood cell), low level of lymphocytes (a type of white blood cell) (lymphopenia is an expected pharmacological effect), weakness, eczema, itching, elevated blood fat levels (triglycerides), hair loss, breathlessness, depression, blurred vision, and hypertension

Uncommon (may affect up to 1 in 100 people):
Neutropenia (low level of a type of white blood cells called neutrophils), depressed mood, and nausea

Rare (may affect up to 1 in 1,000 people):
Blood vessel disorders, nervous system disorders

Not known (frequency cannot be estimated from the available data):
Peripheral swelling

It is important to know that there may be other side effects that are not yet known. Side effects may go away after the treatment is stopped, but it is also possible that side effects may last a long time or may never go away. They may range from mild to severe or even life threatening and/or fatal.

No studies in humans have thus far shown effects to the skin from exposure to sunlight when taking etrasimod. However, caution should be taken as the study compound may increase the risk of redness of the skin, rash, and sunburn.

MOXIFLOXACIN (AVALOX)
Moxifloxacin (Avalox) is known to have the following, most common, side effects: temporary changes in the electrical activity of the heart, palpitations, inflammation of the tendons, fainting spells, dizziness or lightheadedness, allergic reactions and convulsions.

Contacts

Public
Arena Pharmaceuticals, Inc.

Nancy Ridge Drive 6154
San Diego 92121
US
Scientific
Arena Pharmaceuticals, Inc.

Nancy Ridge Drive 6154
San Diego 92121
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- healthy male/female subjects
- 18-55 yrs, inclusive
- BMI: 18.5-30.0 kg/m2, inclusive

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study or being a blood donor within 60 days from the start of the study. In case of donation or loss of more than 1.5 liters of blood (for male subjects) / more than 1.0 liters of blood (for female subjects) in the 10 months prior to the first drug administration in the current study.

Study design

Design

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):	24-05-2017
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Etrasimod
Generic name:	APD334
Product type:	Medicine
Brand name:	Moxifloxacin
Generic name:	N/A
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-05-2017
Application type:	First submission

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	EUCTR2017-001093-42-NL
CCMO	NL61841.056.17