A single dose, randomised, double-blind parallel group study to compare the pharmacokinetics and pharmacodynamics of PB006 with Tysabri® in healthy subjects

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The sponsor is developing a compound (PB006) similar to Tysabri® (natalizumab, hereafter referred to as Tysabri). As part of medical-scientific studies to confirm the similarity of the two compounds, the Sponsor wants to compare PB006 with EU-...

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

Summary

ID

NL-OMON49168

Source
ToetsingOnline

Brief title
PB006/Tysabri bioequivalence study

Condition

- Autoimmune disorders

Synonym
Multiple Sclerosis MS

Research involving
Human

Sponsors and support

Primary sponsor: Polpharma Biologics S.A.
Source(s) of monetary or material Support: Polpharma Biologics S.A.

Intervention

Keyword: Bioequivalence, PB006, PK/PD, Tysabri

Outcome measures

Primary outcome

• To demonstrate pharmacokinetic comparability of PB006 to US-licensed Tysabri® in terms of AUC0-inf of total natalizumab

• To demonstrate pharmacokinetic comparability of PB006 to EU-approved Tysabri® in terms of AUC0-inf of total natalizumab

• To demonstrate comparability pharmacokinetics of US-licensed and EU-approved Tysabri® in terms of AUC0-inf of total natalizumab

• To demonstrate pharmacodynamic comparability of PB006 to pooled reference (US-licensed Tysabri® and EU-approved Tysabri®) in terms of baseline-adjusted AUEC0-12w of CD19+

• To demonstrate pharmacodynamic comparability of PB006 to US-licensed Tysabri® and EU-approved Tysabri® in terms of parameters of α4-integrin receptor saturation

Secondary outcome

• To support pharmacokinetic comparability of PB006 to US-licensed Tysabri® and EU-approved Tysabri® in terms of secondary PK parameters of total natalizumab

• To support pharmacokinetic comparability of PB006 to US-licensed Tysabri® and EU-approved Tysabri® in terms of PK parameters of unexchanged natalizumab

• To support comparability of PB006 to US-licensed Tysabri® and EU-approved Tysabri® in terms of secondary PD parameters of baseline-adjusted CD19+

• To support pharmacodynamic comparability of PB006 with US-licensed Tysabri® and EU-approved Tysabri® in terms of sVCAM decrease

• To support pharmacodynamic comparability of PB006 with US-licensed Tysabri® and EU-approved Tysabri® in terms of sMAdCAM decrease

• To support pharmacodynamic comparability of PB006 to US-licensed Tysabri® and EU-approved Tysabri® in terms of PD parameters of CD34+

• To support comparable immunogenicity profiles of PB006 with US-licensed Tysabri® and with EU-approved Tysabri®

• To support comparable safety and tolerability profiles of PB006 and both US-licensed Tysabri® and EU-approved Tysabri®

Study description

Background summary

The sponsor is developing a compound (PB006) similar to Tysabri. As part of medical-scientific studies to confirm the similarity of the two compounds, the sponsor wants to compare PB006 with EU-approved and US licensed Tysabri.

Tysabri is a drug approved in Europe and the USA for the treatment of Multiple Sclerosis (MS) and in the USA also for the treatment of Crohn*s Disease. MS causes inflammation in the brain that damages the nerve cells. Symptoms of MS can include: walking problems, numbness in the face, arms or legs, problems with vision, tiredness, feeling off-balance or light headed, bladder and bowel problems, difficulty in thinking and concentrating, depression, acute or chronic pain, sexual problems, stiffness, and muscle spasms.

The active ingredient of Tysabri is natalizumab which is an antibody. These antibodies work by binding to proteins in the body so that the harmful effect of that protein is removed. Tysabri stops the cells that cause inflammation

from going into the brain. This reduces nerve damage caused by MS.

Study objective

The sponsor is developing a compound (PB006) similar to Tysabri® (natalizumab, hereafter referred to as Tysabri). As part of medical-scientific studies to confirm the similarity of the two compounds, the Sponsor wants to compare PB006 with EU-approved and US-licensed Tysabri.

The purpose of this study is to investigate how quickly and to what extent PB006 is absorbed and eliminated from the body compared to the EUapproved Tysabri, and US licensed Tysabri. It will also be investigated how the body responds to PB006 compared to the two Tysabri products. In addition, the study will assess the safety and tolerability profiles of PB006 and both Tysabri products.

Study design

The actual study will consist of 1 period during which the volunteer will stay in the research center for 10 days (9 nights). This will be followed by 9 days during which the volunteer will visit the research center for a short visit. These short visits will take place on Day 15, 22, 29, 36, 43, 57, 71, 78, and 85.

The volunteer will receive PB006, EU approved Tysabri, or US-licensed Tysabri as an intravenous infusion over 60 minutes. The dose the volunteer will receive is 3 mg/kg body weight.

Whether the volunteer will receive PB006, EUapproved Tysabri, or US-licensed Tysabri will be determined by chance. PB006, EU approved Tysabri, and US-licensed Tysabri will each be given to 120 volunteers. Neither the volunteer, nor the PI knows which treatment will be dosed.

Intervention

The volunteer will receive PB006, EU approved Tysabri, or US-licensed Tysabri as an intravenous infusion over 60 minutes. The dose he or she will receive is 3 mg/kg body weight.

Study burden and risks

The study compound may cause side effects, though not everybody will be affected.

The following side effect is most often reported (by more than 1 in 10 people) with Tysabri:

- Infusion-related side effects

The following side effects have been reported by up to 1 in 10 people in medicalresearch studies with Tysabri:
- Urinary tract infection
- Sore throat and runny or blocked up nose
- Shivering
- Itchy rash (hives)
- Headache
- Dizziness
- Feeling sick (nausea)
- Being sick (vomiting)
- Joint pain
- Fever
- Tiredness

The following side effects have been reported in a previous clinical study on healthy volunteers with PB006:
- Headache
- Fatigue
- Malaise
- Nausea
- Vomiting

The study compound may also have side effects that are still unknown.

Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising.

During the course of the study (from screening to follow-up), we will take a maximum of 600 milliliters of blood from the volunteer.

To make a heart tracing, electrodes will be pasted at specific locations on the arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

A sample for the coronavirus test will be taken from the back of the nose and/or throat using a swab. Taking the sample only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of your throat may cause the volunteer to gag. When the sample is taken from the back of the nose, you may experience a stinging sensation and the eyes may become watery.

Possible risk of development of progressive multifocal leukoencephalopathy (PML)

JCV is a common virus that is generally harmless to humans and often acquired during childhood. It does not cause symptoms in people whose immune system

functions normally. However, JCV can cause PML in people with weakened immune systems. Causes of a weakened immune system may include HIV infection, leukemia or lymphoma, or taking a medication such as Tysabri. Testing positive for JCV antibodies means that a person has been exposed to JCV in the past.

If the volunteer has been treated with Tysabri or PB006 or with an immunosuppressant medication or in case the volunteer should test positive for JCV, he/she will not be eligible to participate in this study. Therefore, all risk factors for PML will not be present in order to reduce the potential risk as much as possible.

PML is a rare disorder in which the coating (myelin) of brain nerve fibers gets damaged. The most prominent symptoms of PML are clumsiness, progressive weakness, visual changes, speech changes, and sometimes personality changes. PML can result in death or variable degrees of neurological disability. There are no cases of PML known in healthy volunteers without JCV antibodies, after administration of Tysabri or PB006.

In people testing negative for JCV, the incidence of PML is estimated at less than 1 in 10.000. People with all three known risk factors have a greater estimated risk of PML. The risk factors are:
- The presence of anti-JCV antibodies.
- Longer duration of Tysabri treatment, especially beyond 2 years.
- Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. The subject is male/female and 18 to 54 years of age, inclusive
2. The subject is healthy as determined by their medical history, a physical examination, vital signs, an ECG and clinical laboratory testing
3. The subject has a BMI within the range of 18.5 to 30.0 kg/m2, inclusive and a body weight of 50 - 92 kg, inclusive
4. The subject provided written, informed consent prior to any clinical study-specific procedures.
5. Male subject (if his female spouse/partner is of childbearing potential) must confirm that he is using two acceptable methods for contraception during the study and for 3 months after final study drug administration. Male subject should confirm he has informed his partner of participation in the study and the need to avoid pregnancy. Surgically sterilised male subjects do not require additional use of contraception.

Subject needs, after implementation of amendment 3, 2 negative PCR SARS-CoV-2 tests before dosing with natalizumab (after admission to the clinic and prior to dosing).

Further criteria apply

Exclusion criteria

1. Any known exposure to natalizumab, alemtuzumab, ocrelizumab, daclizumab, rituximab, ofatumumab or obinutuzumab or any other B- and T-cell targeting therapies.
2. Any known exposure to immunosuppressive agents
3. Known or suspected hypersensitivity to natalizumab, or any components of the

formulation used
4. Any exposure to steroids prior to dosing, to agents such as interferon-β, glatiramer acetate, fingolimod or laquinimod, to teriflunomide or to dimethyl fumarate
5. Plasma exchange within 3 weeks prior to dosing.

Exclusion of subjects with a history or evidence of SARS-CoV-2 infection in the last month prior screening 1 or having been in confirmed contact with SARS-CoV-2 positive subjects in the last 2 weeks before dosing (after implementation of amendment 3).

Further criteria apply

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-10-2019
Enrollment:	149
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	14-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	25-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-10-2020
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
EudraCT	EUCTR2019-003874-15-NL
CCMO	NL71674.056.19

Study results

Date completed:	21-01-2021
Results posted:	29-10-2021

First publication
28-10-2021