A randomized, double-blind, three-way crossover study to compare the pharmacokinetics, pharmacodynamics and safety of a single 6 mg subcutaneous administration of the proposed biosimilar product LA-EP2006, Neulasta® US and Neulasta® EU in healthy subjects

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

Summary

ID

NL-OMON45253

Source
ToetsingOnline

Brief title
PK bioequivalence, PD equivalence of LA-EP2006, Neulasta US and Neulasta EU

Condition

- Haematological disorders NEC

Synonym
infection, reduced white blood cell count

Research involving
Human

Sponsors and support

Primary sponsor: Hexal AG
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: double-blind, PD, PK, safety

Outcome measures

Primary outcome

The primary objective for this study is to demonstrate PK similarity in terms

of pegfilgrastim AUC0-inf, AUC0-last and Cmax as well as

PD similarity based on ANC AUEC0-last and ANC Emax between:

- LA-EP2006 and Neulasta® US

- LA-EP2006 and Neulasta® EU

- Neulasta® US and Neulasta® EU

following a single 6 mg subcutaneous (s.c.) injection in healthy male and

female subjects.

The PK and PD primary endpoints will be tested as co-primary endpoints for all

pairwise comparisons among LA-EP2006, Neulasta® US and Neulasta® EU. The

similarity for both, PK and PD among the three treatment groups will be

statistically demonstrated only if the 90%

CIs for geometric mean ratios of all co-primary endpoints and for all pairwise

comparisons among LA-EP2006, Neulasta® US and Neulasta® EU are contained within the predefined equivalence margins of 0.8 to 1.25.

Secondary outcome

The secondary objectives of the study are to evaluate/compare LA-EP2006 with Neulasta® US, LA-EP2006 with Neulasta® EU and Neulasta® US with Neulasta® EU following a single 6 mg s.c. injection in healthy male and female subjects in terms of:

- Descriptive statistics for PK (tmax and t1/2), and PD ANC tmax,E parameters.

- Safety, immunogenicity, and local tolerance.

Study description

Background summary

LA-EP2006 is an investigational compound that is being developed as a proposed biosimilar to Neulasta® (the originator*s product). A biosimilar is a compound that is similar to the originator for which the patent has expired. The biosimilar aims to be similar to the originator*s product in terms of activity, safety profile and overall quality. Neulasta® is an approved drug for the treatment of a shortage of white blood cells in order to prevent infections. It is used mostly for patients with cancer to treat the side effects of chemotherapy. Neulasta® is on the market in the US as Neulasta®US and in Europe as Neulasta®EU. The aim for LA-EP2006 is to be approved for the treatment of the same shortage of white blood cells as Neulasta®US and Neulasta®EU.

The active compound of LA-EP2006, Neulasta®US and Neulasta®EU is called pegfilgrastim. This is a protein which is very similar to the human protein called *granulocyte colony stimulating factor* (also known as G-CSF or filgrastim). G-CSF is naturally present in the human body. Therefore, pegfilgrastim is called a *biological*. The difference between naturally occurring G-CSF and pegfilgrastim is the attachment of a large chain of molecules (a polymer called polyethylene glycol) to the protein. This makes the protein stay longer in the body so patients need to receive drug less often to achieve the same effect. LA EP2006 is a new pegfilgrastim strongly resembling Neulasta®US and Neulasta®EU. These 3 compounds are produced with the help of bacteria which have received a small piece of human DNA which makes them able

to produce the active protein. LA-EP2006 has not been approved as a drug, but has been given to humans before in other studies.

Study objective

The purpose of the study is to compare LA-EP2006 and Neulasta®US and Neulasta®EU with respect to how quickly and to what extent the compounds are absorbed and eliminated from the body after injection under the skin of the abdomen (this is called pharmacokinetics). It will also investigate the effect of the compounds on the amounts of certain types of white blood cells (this is called pharmacodynamics) and the possible development of antibodies against pegfilgrastim in the volunteers blood. Finally it will be investigated to what extent the compounds are safe and tolerated.

Study design

This is a randomized double-blind single-dose, three treatments, six sequence crossover, PK/PD study with three Treatment Periods (Treatment Periods I, II and III) in 576 healthy male and female subjects. The study duration for an individual subject will be approximately 25 weeks (up to 5 weeks of screening followed by at least 20 weeks of treatment, assessment and washout periods). Dosing in Treatment Period I and II will be followed by at least 8 week washout period, including a 4 week assessment period. Dosing in Treatment Period III will be followed by a 4 week assessment period only.

Intervention

The volunteer will receive one single injection of 6 mg LA-EP2006 diluted in 0.6 mL solution during one period, one single injection of 6 mg Neulasta®US diluted in 0.6 mL solution during other period and one single injection of 6 mg Neulasta®EU diluted in 0.6 mL solution during another period.

Study burden and risks

LA-EP2006 has been studied before in research similar to the current study. The most frequently observed adverse effects in man were similar to the side effects described below for Neulasta® (US and EU). The volunteers should be aware that the aforementioned adverse effects and possibly other, still unknown adverse effects, may occur during the study. If this is the case, the volunteers will be given all new information that may affect their willingness to start or continue in the study. However, with the doses used in this study serious adverse effects are uncommon.

Neulasta® has been used now for 14 years and is registered as a drug in over 100 countries worldwide. The following list represents most of the side effects known for pegfilgrastim, reported by cancer patients who received multiple

doses of pegfilgrastim to treat the side effects of chemotherapy. Because this study includes only healthy volunteers who will receive single doses of LA-EP2006 and Neulasta®US and Neulasta®EU), probability of any of the following events to happen is considered low in this study.

Very common side effects (may affect more than 1 in 10 people):
• Bone pain, and general aches and pains in the joints (painkillers will be offered as needed, as judged by the responsible doctor).
• Nausea and headaches.

Common side effects (may affect up to 1 in 10 people, but in more than 1 in 100 people):
• Pain and redness at the site of the injection.
• Musculoskeletal pain
• Some changes may occur in the blood, but these will be detected by routine blood tests. The volunteer's white blood cell count may become high for a short period of time. Their platelet count may become low which might result in bruising.

Uncommon (may affect up to 1 in 100 people, but in more than 1 in 1000 people):
• Allergic-type reactions, including redness and flushing, skin rash, and raised areas of the skin that itch.
• Injection site reaction.
• Sickle cell crisis in patients with sickle cell anemia.
• An increase in various laboratory markers as uric acid, liver enzymes, lactate dehydrogenase and alkaline phosphatase.
• Serious allergic reactions, including anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face).
• Increased spleen size or rupture. Some cases of splenic rupture were fatal.
• A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).
• Sweet*s syndrome (plum-colored, raised, painful lesions on the limbs and sometimes the face and neck with fever) has occurred but other factors may play a role.
• Cutaneous vasculitis (inflammation of the blood vessels in the skin).
• Kidney injury (glomerulonephritis).
• Capillary Leak Syndrome; the study compound can cause fluid to leak from blood vessels into your body*s tissues. This condition is called *Capillary Leak Syndrome*.

Vomiting, nausea, oropharyngeal pain, feeling hot, malaise, palpitations, ear pain, tooth ache, hot flushes, ocular erythema and nasopharyngitis were also experienced in several other studies. In patients with breast cancer the following adverse events were reported: vomiting, nausea, stomatitis, anemia, decreased appetite, abdominal pain, alopecia, fatigue, myalgia, arthralgia, pyrexia, weakness (asthenia), leukopenia (a decrease of white blood cells), thrombocytopenia (a decrease in platelet counts), cough, pain in the extremity, bone pain and headache.

It should be emphasized that the most common side effects could still be present or may appear on the day the volunteer leaves the clinical research center.

LA-EP2006 and Neulasta® (US and EU) are so-called *biologicals*; given the properties of these drugs, there is a chance that your body will develop antibodies against filgrastim, pegfilgrastim and PEG or that a hypersensitivity reaction will be induced. This chance is very small, as antibody development to (peg)filgrastim occurs in only 3% of the cases. In addition, there is no scientific evidence that these antibodies will block the effect of the study compound.
However, theoretically this means that if antibody development occurs and you should need filgrastim or pegfilgrastim as therapy in the future, your response to treatment by this drug may be reduced or absent, and/or you may get a hypersensitivity reaction. This chance however is very small.
Filgrastim and pegfilgrastim are in clinical use extensively for more than 10 years. According to current knowledge, there seems to be no reason to believe that administration of pegfilgrastim or its biosimilars hampers the possible future use of these agents.

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

- healthy male and female volunteers
- age 18 - 55 years, inclusive
- BMI 19.0 - 30.0 kg/m2, inclusive
- weight >= 60 kg

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 12 weeks from the start of the study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-04-2017
Enrollment:	136
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Neulasta EU
Generic name:	pegfilgrastim
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Neulasta US
Generic name:	pegfilgrastim
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2018
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	EUCTR2016-003549-27-NL
CCMO	NL60723.056.17