An open label, single dose study to assess the pharmacokinetics of a microdose of recombinant human placental alkaline phosphatase (hRESCAP, part 1) followed by a randomized, double-blind, placebo-controlled, parallel, single ascending dose, first-in-human study to assess safety and tolerability of hRESCAP (part 2) in healthy male volunteers

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Part 1:- To assess the PK of a single iv microdose (

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

Summary

ID

NL-OMON38993

Source
ToetsingOnline

Brief title
PK, safety and tolerability of hRESCAP in healthy male volunteers

Condition

- Autoimmune disorders
- Bacterial infectious disorders

Synonym
inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Alloksys Life Sciences bv,TNO

Intervention

Keyword: Alkaline phosphatase, First-in-Human, Microdose

Outcome measures

Primary outcome

Tolerability / Safety endpoint

- Assessment of adverse events, local tolerability, vital signs, clinical

chemistry and haematology parameters.

Pharmacokinetic endpoints

- Assessment of PK after microdose administration of 53 µg [14C]-hRESCAP;

- Determination of the half-life of [14C]-hRESCAP within pharmacological

relevant dose-range (414-5300 µg).

Pharmacodynamic endpoints

- Assessment of the total alkaline phosphatase activity by standard assay;

- Determination of placental alkaline phosphatase activity with an assay

specific for placental alkaline phosphatase.

Secondary outcome

N/A

Study description

Background summary

Alkaline phosphatase (AP) is a common endogenous enzyme, which is present in many cells and/or organs in the human body (e.g. intestine, placenta, liver, bone, kidney and neutrophilic granulocytes). Although the role of this enzyme is not fully elucidated, there is growing evidence that AP plays a significant role in host defence and innate immunity, particularly against inflammatory reactions due to release of endotoxin and other phosphorylated pro-inflammatory substrates (e.g. extracellular nucleotides).
Various forms of AP exist. Bovine Intestinal Alkaline Phosphatase (BIAP) was developed with the intention to prevent acute ischemia-reperfusion mediated inflammation. From all studies in animal species and humans it was concluded that bovine AP is well tolerated in species that are tolerant for this bovine protein. For chronic inflammatory disease Alloksys developed a recombinant placental alkaline phosphatase with more favorable plasma kinetics (e.g. a longer half-life), compatible to routine use therapeutic applications.
Therapeutic targets are patients suffering from disease like Rheumatoid Arthritis (RA), asthma, and Multiple Sclerosis (MS) that are either resistant to classic disease-modifying antirheumatic drugs (DMARDS) pharmaceuticals like methotrexate (MTX) or those that are tolerant to biological TNF-α blocker products. Due to its different mode of action (MOA) hRESCAP is considered to be an alternative to these TNF-α blockers. Application of hRESCAP as single therapeutic entity is foreseen, albeit that due to its different MOA also combination treatment with classic pharmaceuticals or TNF-α blockers will be enabled as well. It is understood that this hRESCAP may be applied as well in acute settings.

Study objective

Part 1:
- To assess the PK of a single iv microdose (<=30 nmol) of recombinant human placental alkaline phosphatase (hRESCAP);

- To assess if microdosing is a suitable technique to predict the PK of recombinant proteins using hRESCAP as model in humans at pharmacologically relevant doses (in combination with the results obtained in part 2);

Part 2:
- To determine the safety and tolerability of single iv dose of hRESCAP in doses up to 5300 µg in healthy volunteers;

- To determine the pharmacokinetics and pharmacodynamics of ascending iv doses of hRESCAP in healthy volunteers within a pharmacologically relevant dose-range and compare this with BIAP pharmacokinetics with emphasis on half-life (t1/2).

Study design

Part 1: An open label study of single doses of hRESCAP administered intravenously to healthy male volunteers.
Part 2: A randomized, double-blind, placebo-controlled, parallel, first-in-human study of single ascending doses of hRESCAP administered intravenously to healthy male volunteers.

Intervention

Part 1
Group 1: 53 µg 14C-hRESCAP

Part 2
Group 2: 414 µg 14C-hRESCAP / matching placebo
Group 3: 2480 µg 14C-hRESCAP / matching placebo
Group 4: 5300 µg 14C-hRESCAP / matching placebo

Study burden and risks

Of investigational products that have not been administered to humans before such as hRESCAP, not all adverse events are known and unexpected adverse events could occur such as hypersensitivity reactions.

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. Healthy male subjects, 18 - 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis;
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive;
3. Ability to communicate well with the investigator in the Dutch language;
4. Able to participate and willing to give written informed consent and to comply with the study restrictions;
5. Venous access sufficient to allow blood sampling as per protocol.

Exclusion criteria

1. Any clinically significant abnormality as determined by medical history taking and physical examinations obtained during the screening visit that in the opinion of the investigator would interfere with the study objectives or compromise subject safety;
2. History of a surgical event that may significantly affect the study outcome;
3. History of allergy or other inflammatory indications;
4. History of asthma or other inflammatory disease;
5. Use of prescription medications within 21 days prior to study drug administrations, or less than 5 half-lives, whichever is longer, and during the course of the study.
6. Alkaline Phosphatase levels in plasma of < 30 IU/L or > 115 IU/L;
7. Clinically relevant abnormal laboratory results, ECG, vital signs, or physical findings at screening that in the opinion of the investigator would interfere with the study objectives or compromise subject safety;

8. Participation in an investigational drug study within 3 months prior to screening or more than 4 times in the past year;
9. Any psychological conditions which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol;
10. History of alcohol or illicit drug abuse (alcohol abuse defined as alcohol consumption > 28 units/week);
11. Reported unexplained weight loss or weight gain of > 2 kg in the month prior to screening;
12. Positive test results for Hepatitis B, Hepatitis C or HIV;
13. Donation of blood within 3 months prior to screening or donation of plasma within 14 days prior to screening;
14. Not having a general practitioner;
15. Not willing to accept information transfer which concerns participation in the study, or information regarding health, like laboratory results, findings at anamnesis or physical examination and eventual adverse events to and from his general practitioner;
16. Not willing to give permission to have the general practitioner to be notified upon participation in this study;
17. Prior participation in part 1 for subjects participating in part 2 of the study;
18. Not willing to use effective (double barrier) contraception until at least 3 months after dose administration.

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):	19-06-2013
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	recombinant human placental alkaline phosphase (labelled with 14C)

Ethics review

Approved WMO Date:	07-05-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2013
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	EUCTR2013-001814-13-NL
CCMO	NL44653.056.13