A pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still*s Disease (AOSD) developing Macrophage Activation Syndrome/ secondary HLH (MAS/sHLH)

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

Summary

ID

NL-OMON50760

Source
ToetsingOnline

Brief title
NI-0501-06

Condition

- Autoimmune disorders
- Joint disorders

Synonym
complication of Juvenile Idiopathic Arthritis [sJIA] or Adult-onset Still□s Disease (AOSD), Macrophage Activation Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Swedish Orphan Biovitrum AG
Source(s) of monetary or material Support: Sobi AG

Intervention

Keyword: emapalumab, MAS, Open-Label

Outcome measures

Primary outcome

Pharmacokinetics and Pharmacodynamics

* PK profile of emapalumab.

* Levels of circulating free IFNγ- at predose, and total IFNγ (free IFNγ+bound

to emapalumab) after initiation of emapalumab.

* Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10).

* Correlation between chemokine levels (CXCL9, CXCL10) and levels of free

emapalumab, free IFNγ (pre-dose) and total IFNγ (exploratory analysis).

* Correlation of chemokine and total IFNγ levels, and laboratory parameters of

MAS severity, e.g. ferritin, platelet count, LFTs (exploratory analysis).

* Levels of other potential disease markers (e.g. sCD25, sCD163, IL-10, IL-6,

IL-18, TNFα).

* Levels (if any) of circulating antibodies against emapalumab to determine immunogenicity (ADA).

In particular, based on:

* levels of circulating emapalumab

* levels of total IFNγ

* levels of main IFNγ-induced chemokines (namely CXCL9 and CXCL10)

a PK/PD modelling will be used to confirm that the proposed dose regimen is adequate in relation to the IFNγ production in this patient population.

Safety

The tolerability and safety of emapalumab treatment will be assessed as follows:

* Incidence, severity, causality and outcomes of AEs (serious and non-serious), with particular attention being paid to infections.

* Evolution of laboratory parameters, in particular CBC, LFTs, inflammatory markers (ferritin and CRP) and coagulation parameters.

* Number of patients withdrawn from the study due to safety reasons.

Efficacy

An assessment of emapalumab efficacy in this patient population will be based on the following variables:

* Number of patients achieving MAS remission by Week 8 after initiation of emapalumab treatment.

* Time to MAS remission.

* Number of patients for whom at any time during the study glucocorticoids can be tapered i) to the same (or lower) dose being administered before the occurrence of MAS (in those patients who are already treated for the underlying

condition) or ii) by 50% (or less) of the dose administered at emapalumab treatment start (in those patients who present with MAS at disease onset).

* Time to glucocorticoids tapering (as above described).

* Survival time.

* Number of patients withdrawn from the study due to lack of efficacy.

Secondary outcome

* All study variables are considered to be exploratory in this study, and no hierarchy of endpoints has been specified, as the objective of this pilot study is to collect and analyze data to confirm that the proposed dose regimen is adequate in this patient population. Statistical methods will therefore focus on summarizing the data collected using descriptive statistics and on appropriate graphical presentations.

* For binary endpoints (MAS remission by Week 8, number of patients who taper glucocorticoids, number of patients who discontinue due to lack of efficacy), 95% confidence intervals will be calculated for proportions.

* For time to event endpoints (time to MAS remission, time to achievement of glucocorticoids tapering and time to death), Kaplan-Meier curves will be calculated and summary statistics, such as medians, proportions event-free at various time points will be calculated and presented, and 95% confidence intervals calculated where possible.

* Data relating to safety will be listed and summarised using descriptive statistics.

Study description

Background summary

The condition, MAS, is an illness in which there is a disproportionate multiplication and activation of some cells responsible for controlling the mechanisms of defense of the body (the immune system). Although they are found in large numbers, these specific cells are unable to eliminate microbes and viruses, but produce large quantities of molecules which cause exaggerated inflammation within the body. This can cause extensive harm to the tissues and organs and is a threat of life. To fight against this exaggerated inflammation an urgent and aggressive treatment and constant medical supervision is required.

The experimental study treatment, emapalumab, has been created by a biotechnology company, Sobi AG. The study treatment is a protein similar to other proteins the body produces to fight against foreign substances or infections.
Emapalumab has been selected because it inactivates a protein called interferon gamma (IFNγ) which is believed to be responsible for the inflammation and tissue damage in MAS patients. Therefore, by neutralizing IFNγ, the inflammation present in the body may be halted, stopping organ damage and restoring a healthier condition.
Emapalumab has already been given to 14 healthy adults and more than 30 children, up to a dose of 10 mg/kg in some patients.

Study objective

The aim of this study is to investigate how safe, effective, and well-tolerated multiple infusions of the experimental study treatment, emapalumab (the study medication) are in controlling this disease, as well as to check the concentrations of emapalumab in blood and the speed at which it leaves the body.The study treatment will be administered in combination with a steroid (e.g., methylprednisolone). This study has an optional genetic research part.

The main objectives of the study are:
* To describe the pharmacokinetics (PK) profile of emapalumab.
* To confirm the proposed dosing regimen of emapalumab.
* To evaluate the safety and tolerability profile of intravenous (i.v.) administrations of emapalumab.
* To preliminary assess the efficacy of emapalumab.
* To assess the levels of relevant markers, such as IFN* and main IFN*-induced chemokines (CXCL9, CXCL10).
* To assess other potential disease markers (e.g. sCD25, sCD163, IL-10, IL-6, IL-18, TNFα).
* To assess the immunogenicity of emapalumab.

Study design

Interventional Phase 2 study
Open-label, single arm, international, multicenter study.

Intervention

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Study burden and risks

As long as the study treatment is present in blood, there are potential risks linked to it:

• an infection may be picked up more easily than in a normal health status or an infection in the past may come back, due to the action of the study treatment on the immune system. This risk is already present as a result of this condition and of some other medications/treatments that were previously received or will be received for this condition, which also reduce the body*s ability to fight infections. To minimise this risk, receiving preventative medications will be continued as long as the study treatment is measurable in the body. The study doctor will pay particular attention to monitor for any signs of infection during the course of the study.
• The study treatment may have an interfering effect on vaccinations. It is important to discuss with the study doctor if there is a need to have any vaccinations as long as the activity of the study treatment emapalumab can be detected in the blood.
• Since the study treatment is a protein that has not been produced by the body, its introduction into blood might provoke production of antibodies against it. To detect the occurrence of these antibodies against the study treatment, blood analysis will be performed from time-to-time during the study.

During, or shortly after, the infusion:
• The study treatment could cause an allergic reaction (e.g., rash), as could any other protein-based medication. However, these reactions usually occur after the first infusions. Since during and after the infusion there will be close medical supervision, and immediate medical care will be received.
• The study treatment will be given through a central line (a long thin tube which the study doctor will have placed in a vein in the chest through an insertion point in the neck), to avoid multiple needle insertions whenever possible. This is usually done under local anaesthetic to numb the area. The study treatment administration will take approximately 1-2 hours and will be closely monitored by a study doctor.
• Local inflammation at the infusion site, if a central line is not used: symptoms could include warmth, redness, itching, bruising, swelling and pain at

the cannula site. This risk should be avoided by careful infusion monitoring, which is planned in the study.

As the study treatment is an investigational medication, there might be side effects that are not been yet identified.

You will find further information on risks related to study procedures in Appendix E (see Informed Consent Form)

Contacts

Public
Swedish Orphan Biovitrum AG

Ch. des Aulx 12
Plan-les-Ouates 1228
CH
Scientific
Swedish Orphan Biovitrum AG

Ch. des Aulx 12
Plan-les-Ouates 1228
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients of both genders 2. For sJIA patients: confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA high presumption of sJIA (as per Appendix A) will suffice for eligibility.AOSD patients: confirmed AOSD diagnosis as per Yamaguchi criteria (Appendix E) 3. Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the followings:
Febrile patient presenting with:
- Ferritin > 684 ng/mL
and any two of:
- Platelet count <= 181 x10^9/L
- AST levels > 48 U/L
- Triglycerides > 156 mg/dL
- Fibrinogen levels <= 360 mg/dL.
(see Appendix B), 4 Patient presenting an inadequate response to high dose i.v. glucocorticoid treatment administered for at least 3 days as per local standard of care (including but not limited to pulses of 30 mg/kg methylprednisolone (mPDN) on 3 consecutive days).
High i.v. glucocorticoid dose should not be lower than 2 mg/kg/ day of PDN equivalent in 2 divided doses, (or at least 60 mg/day in patients of 30 kg or more) In case of rapid worsening of the patient*s condition and/or lab parameters, inclusion may occur within less than 3 days from starting high dose i.v. glucocorticoids. 5.Tocilizumab, TNF inhibitors and canakinumab, if administered, have to be discontinued before emapalumab initiation. 6. Informed consent provided by the patient (as required by local law), or by the patient*s legally authorized representative(s) with the assent of patients who are legally capable of providing it, as applicable. 7. Having received guidance on contraception for both male and female patients sexually active and having reached puberty:
Females of child-bearing potential require use of highly effective contraceptive measures (failure rate of less than 1% per year) from screening until 6 months after receiving last dose of the study drug.
Highly effective contraceptive measures include:
o Sexual abstinence
o Hormonal contraceptives: combination or progesterone only
o Intrauterine methods: intrauterine devices or systems
o Bilateral tubal occlusion
o Vasectomised partner
Males with partners(s) of child-bearing potential must agree to take appropriate precautions (such as sexual abstinence, barrier contraception, vasectomy) to avoid fathering a child from screening until 6 months after receiving last dose of the study drug.

Exclusion criteria

1. Diagnosis of suspected or confirmed primary HLH or HLH consequent to a neoplastic disease. 2.Active mycobacteria (typical and atypical), Histoplasma Capsulatum, Shigella, Salmonella, Campylobacter and Leishmania infections., 3. Clinical suspicion of latent tuberculosis., 4. Positive serology for HIV antibodies., 5. Presence of malignancy., 6. Patients who have another concomitant disease or malformation severely affecting the cardiovascular, pulmonary, CNS, liver or renal function that in the opinion of the Investigator may significantly affect likelihood to respond to treatment and/or assessment of emapalumab safety., 7. History of hypersensitivity or allergy to any component of the study drug., 8. Receipt of a BCG vaccine within 12 weeks prior to screening., 9. Receipt of live or attenuated live vaccines (other than BCG) within 6 weeks prior to screening., 10. Pregnant or lactating female patients.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2018
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Emapalumab
Generic name:	na

Ethics review

Approved WMO Date:	13-02-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2016-004223-23-NL
ClinicalTrials.gov	NCT03311854
CCMO	NL61939.041.17

Study results

Results posted: 28-10-2021

First publication
15-10-2021