A two-cohort, open-label, single arm, multicenter study to evaluate efficacy, safety and tolerability, pharmacokinetics and pharmacodynamics, of emapalumab in children and adults with macrophage activation syndrome (MAS) in Still*s disease (including systemic juvenile idiopathic arthritis and Adult onset Still*s disease) or with MAS in Systemic lupus erythematous

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

Summary

ID

NL-OMON52297

Source
ToetsingOnline

Brief title
NI-0501-14

Condition

- Autoimmune disorders

Synonym
macrophage activation syndrome, MAS

Research involving
Human

Sponsors and support

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

Intervention

Keyword: macrophage activation syndrome, MAS, Still□s disease

Outcome measures

Primary outcome

Primary efficacy endpoint:

• Proportion of patients with complete response (CR) at Week 8 after first administration of emapalumab.

Secondary outcome

Secondary endpoints:

• GCs tapering to a dose < 50 % of prednisolone (PDN) equivalent at the time of emapalumab start or to the same (or lower) dose being administered before the occurrence of MAS (in patients already treated for the underlying condition) whichever occurs first at any time during the study.

• GCs tapering to <=1mg/kg/day of PDN equivalent at any time during the study.

• Time to achieve GCs tapering (as defined in the 2 bullets above).

• Time to first CR.

• Proportion of patients with OR as defined by CR or partial response (PR).

• Time to first OR as defined by CR or PR.

• MAS recurrence at any time after achievement of CR

• Withdrawal from the study due to lack of response as per Investigator

decision.

• Survival time.

Study description

Background summary

MAS will lead to an abnormally high production of interferon gamma (IFNγ), a protein which is believed to be responsible for too much inflammation within the body. This inflammation can cause a lot of harm to your tissues and organs and can be responsible of high temperature (fever), joint pains, bleeding and increase in the size of some of the body organs such as the liver. The inflammation may also lead to other serious complications in your organs and can be life threatening.
To fight against this exaggerated inflammation, an urgent and aggressive treatment and constant medical supervision is required.
To date, there is no specific medical treatment against MAS approved by any health authority especially if the disease is not controlled with the high dose of corticosteroid medication.
Emapalumab may neutralize the effects of this inflammatory protein (IFNγ) and aims to reduce and/or remove the inflammation in your body, stopping organ damage and trying to restore a healthier condition.

Study objective

This study has been transitioned to CTIS with ID 2024-516153-52-00 check the CTIS register for the current data.

Primary objective:

To demonstrate efficacy of emapalumab in the treatment of patients in:
• Cohort 1: Macrophage activation syndrome (MAS) in the context of systemic juvenile idiopathic arthritis (sJIA) and adult onset Still*s disease (AOSD).
• Cohort 2: MAS in the context of pediatric and adult systemic lupus erythematosus (SLE).

Secondary objectives:
• To demonstrate efficacy of emapalumab with respect to tapering of glucocorticoids (GCs).
• To evaluate the time to onset of response to emapalumab treatment.
• To evaluate efficacy of emapalumab with respect to overall response (OR).
• To evaluate the sustained efficacy of emapalumab treatment.
• To evaluate the patient*s survival after treatment with emapalumab.
• To evaluate the safety and tolerability of emapalumab.
• To evaluate patient-reported outcome of MAS in patients treated with emapalumab.
• To determine the pharmacokinetic (PK) profile of emapalumab.
• To determine the pharmacodynamic (PD) profile of emapalumab.
• To determine the immunogenicity of emapalumab.

Exploratory objectives:
• To explore the correlation between PD parameters and relevant laboratory parameters per cohort.

Study design

Study NI-0501-14 is an open-label 2-cohort, single arm, multicenter, interventional, phase 2/3 study.
The study enrolls pediatric and adult patients between 6 months and 80 years of age with different etiologies of MAS. The patients will be assigned to different cohorts as per their underlying disease:
• Cohort 1: MAS in the context of sJIA and AOSD.
• Cohort 2: MAS in the context of pediatric and adult SLE.
Each cohort in this study is designed as a single arm study and will be composed of 2 phases: one Run-in phase and one Interventional phase.
The Run-in phase will enroll patients as defined in Cohorts 1 and 2, and requiring treatment with GCs. These patients will be treated as per Investigator decision. Patients will be followed for a maximum of 12 weeks, or until reaching a MAS remission as per Investigator assessment, or until presenting an inadequate response to GCs as assessed by the Investigator, whichever occurs first.

Every effort should be taken to enroll patients starting from the Run-in phase (i.e., before starting treatment with GCs). However, it should be noted that this phase is not compulsory, therefore patients can join the study directly in the Interventional phase. Patients who also failed GCs plus other MAS therapies and meet all the eligibility criteria may be enrolled in the Interventional

phase. If at any time during the Run-in phase, patients present an inadequate response to GCs and additionally meet all eligibility criteria of the Interventional phase, they will be invited to continue into the Interventional phase of the study.
Enrollment in the Run-in phase will be achieved when the last patient of the Interventional phase is enrolled. At the time of completion of enrollment into the Interventional phase, patients completing the Run-in phase will not be denied treatment with emapalumab and enrollment into the Interventional phase if needed, and upon fulfillment of all eligibility criteria.
A re-treatment with emapalumab is allowed during the Long-term follow-up period of the study if patients present a recurrence of MAS.
An interim analysis assessing efficacy will be performed after 16 treated patients in Cohort 1 have reached 8 weeks after first dose of emapalumab, or earlier if the patients discontinued the study. Enrollment in Cohort 1 may be closed upon results of this interim analysis. The data from the interim analysis will be used for regulatory submission purposes.

Intervention

Patients enrolled in the Interventional phase will receive emapalumab. Emapalumab will be administered by i.v. infusion at an initial dose of 6 mg/kg over a period of 1 to 2 hours depending on the volume to be infused. Emapalumab treatment will be continued at the dose of 3 mg/kg
every 3 days until Study Day 16 (SD16), and then twice-a-week for additional 2 weeks, i.e., until SD28

Study burden and risks

Please refer to the ICF for risks and discomforts associated with study medication and study procedures.

Contacts

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Scientific
Swedish Orphan International

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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)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Inclusion criteria
Run-in phase in all cohorts
1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
2. Male and female patients aged between 6 months and 80 years of age at the time of diagnosis of active MAS.
3. MAS defined as per the criteria defined below for each cohort and requiring treatment with GCs as per standard of care.
Interventional phase in all cohorts
1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
2. Male and female patients aged between 6 months and 80 years of age at the time of diagnosis of active MAS.
3. Patients who have shown an inadequate response to high dose intravenous (i.v.) GCs administered for at least 3 days according to local standard clinical practice, including but not limited to pulses of 30 mg/kg methylprednisolone (mPDN) on 3 consecutive days. High i.v. GCs dose is recommended not to be lower than 2 mg/kg/ day PDN equivalent (or at least 60 mg/day in pediatric patients of 30 kg or more and at least 1 g/day in adult MAS patients). In case of rapid worsening of the patient*s condition and/or

laboratory parameters, as per Investigator judgment, inclusion may occur within less than 3 days from starting high dose GCs.
4. Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the followings:
a. Febrile patients presenting with ferritin > 684 ng/mL.
b. and any 2 of:
i. Platelet count <= 181 x109/L
ii. Aspartate aminotransferase (AST) -level > 48 U/L
iii. Triglycerides > 156 mg/dL
iv. Fibrinogen level <= 360 mg/dL
5. Female patients of child-bearing potential (sexually or non sexually active). Female patients who are sexually active must be willing to use highly effective methods of contraception from study drug initiation to 6 months after the last dose of study drug.
Specific inclusion criteria for Cohort 1 and Cohort 2
6. Cohort 1:
a. Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA will suffice for eligibility.
b. Confirmed diagnosis of AOSD as per Yamaguchi criteria (Yamaguchi et al. 1992).
7. Cohort 2:
a. Confirmed diagnosis of SLE as per Systemic Lupus International Collaborating Clinics (SLICC) 2012-criteria.

Exclusion criteria

1. Primary hemophagocytic lymphohistiocytosis (pHLH) documented by either the presence of a known causative genetic mutation or abnormal perforin expression or CD107a degranulation assay as described with pHLH or by the presence of family history.
2. Confirmed malignancy. Note: patients with a suspected malignancy should have mononuclear cells typed by flow cytometry and/or tissue biopsy, as applicable, to rule out malignancy.
3. Treatment with canakinumab, Janus kinase (JAK) inhibitors, tumor necrosis factor (TNF) inhibitors and tocilizumab at the time of emapalumab initiation.
4. Ongoing treatment with anakinra at a dose above 4 mg/kg/day at time of emapalumab initiation.
5. Patients treated with etoposide for MAS in the last 1 month.
6. Presence of any medical or psychological condition or laboratory result that in the opinion of the Investigator can interfere with the patient's ability to comply with the protocol requirements or makes the patient not appropriate for inclusion to the study and treatment with emapalumab.
7. Foreseeable inability to cooperate with given instructions or study procedures.
8. Clinically active mycobacteria (typical and atypical), Histoplasma

Capsulatum, or Salmonella infections.
9. Evidence of leishmania infections.
10. Evidence of latent TB.
11. History of hypersensitivity or allergy to any component of the study drug.
12. Receipt of a Bacillus Calmette-Guerin (BCG) vaccine within 12 weeks prior to Screening.
13. Receipt of a live or attenuated live (other than BCG) vaccine within 4 weeks prior to Screening.
14. Pregnancy 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:	Recruiting
Start date (anticipated):	22-09-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Emapalumab
Generic name:	-

Ethics review

Approved WMO

Date:	21-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-08-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2024
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
EU-CTR	CTIS2024-516153-52-00
EudraCT	EUCTR2021-001577-24-NL
ClinicalTrials.gov	NCT05001737
CCMO	NL78647.041.21