A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/ dosing frequency reduction and open-label long term treatment epochs

Published: 23-07-2014
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44251

Source
ToetsingOnline

Brief title
CACZ885N2301 (CLUSTER)

Condition

- Other condition
- Congenital and hereditary disorders NEC

Synonym

hereditary periodic fevers; periodic fevers

Health condition

erfelijke periodieke koortssyndromen (TRAPS, HIDS of crFMF)

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: Canakinumab, Hereditary Periodic Fevers, Interleukin-1

Outcome measures

Primary outcome

Physician*s global assessment of disease activity.

Secondary outcome

CRP, SAA, responders in Epoch 2 who maintain a clinically meaningful response

when switched to canakinumab every 8 weeks compared to placebo in epoch 3.

Adverse events. PK/PD.

Study description

Background summary

Hereditary Periodic Fevers is a group of rare orphan diseases and consists of 4 separate conditions: Cryopyrin Associated Periodic Syndrome (CAPS), TNF receptor Associated Periodic Syndrome (TRAPS), Hyper IgD Syndrome (HIDS) and Familial Mediterranean Fever (FMF). There are currently no approved treatments for TRAPS, HIDS and colchicine resistant FMF (crFMF).
A key feature of these conditions is the recurrent episodes of systemic inflammation with high fever that is accompanied by characteristic signs and symptoms like serositis, neutrophilic rash, muco-cutaneous ulcers, arthralgia/arthritis, and aseptic meningitis/headaches.

Canakinumab is a fully human monoclonal anti-human interleukin-1* (IL-1*) antibody. Canakinumab is designed to bind to human IL-1* blocking the interaction of this cytokine to its receptors, thus functionally neutralizing the bioactivity of this cytokine, IL-1* is recognized as one of the principal pro inflammatory cytokines in a variety of inflammatory conditions. Canakinumab is registered for the treatment of adults with CAPS, gout and of Systemic Juvenile Idiopathic Arthritis.
The purpose of this study is to determine whether canakinumab is able to induce and maintain a clinically meaningful reduction of disease activity in a greater proportion of patients with TRAPS, HIDS, or crFMF compared to placebo. It is further to determine whether, in patients responding to the initial dosing regimen, canakinumab will maintain its clinical efficacy if administered at a reduced dosing interval.
The study protocol allows the inclusion of minors.

Amendment 2 is issued to address the request from the Paediatric Committee at the EMA in to include patients >28 days in this clinical trial compared to previously *2 years of age. Patients >28 days but <2 years old will enter the study directly into the open-label arm of Epoch 2, but won*t be considered toward the total number of patients enrolled for the primary efficacy and safety analyses. In addition, this amendment provides more clarity on patient*s management for randomized and non- andomized cohorts in accordance with clinical practice.
It is unlikely that patients <2 years will be included in NL.

Study objective

Primary: The primary objective of the randomized treatment epoch and for the overall study is to demonstrate that subcutaneous canakinumab administered every 4 weeks is superior to placebo in achieving a clinically meaningful reduction of disease activity defined as resolution of the index flare at Day 15 and no new disease flares over 16 weeks of treatment.
Secondary:
* Percentage of patients who achieve a Physician Global Assessment of Disease Activity <2 (*minimal* or *none*) at Week 16
* Percentage of patients with the serologic remission at Week 16 (defined as CRP <10 mg/L)
* Percentage of patients with normalized Serum Amyloid A level at Week 16 (defined as SAA <10 mg/L)
* Percentage of responders in Epoch 2 who maintain a clinically meaningful response (absence of new flares) when switched to canakinumab every 8 weeks compared to placebo in epoch 3
* Long-term safety and tolerability and immunogenicity
* Pharmacokinetics/pharmacodynamics

Study design

This study consists of 3 cohorts (one cohort per condition: TRAPS, HIDS and crFMF), and 4 study epochs.
Each cohort will follow the same study design across the 4 epochs:
1. Screening (max 12 weeks).
2. A randomized treatment epoch (canakinumab s.c. every 4 weeks versus placebo) of 16 weeks which will provide efficacy and safety data in a double-blind placebo-controlled parallel-arm setting. This randomized treatment epoch will include 2 possible escape options:
* Blinded escape.
* Open-label treatment.
3. A randomized withdrawal epoch of 24 weeks for responders.
4. An open-label treatment epoch of 72 weeks to collect long-term safety data for canakinumab.
180 patients (25 in NL).

Intervention

Treatment with canakinumab (in double blind epoch canakinumab or placebo).

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Study duration approx. 2 years. 25 visits.
Injections with canakinumab/placebo every 4 weeks during approx. 88 weeks (if no withdrawal in epoch 3). In case of dose increase 2 injections per visit. In case of withdrawal: injections every 8 weeks during 24 weeks.
Physical examination approx. 22 times.
Blood tests (approx. 17 ml/visit for adults) approx. 24 times. For children the amount of blood to be taken will be adjusted.
ECG 5 times.
Questionnaires (SF12 en Sheehan disability) 6 times.
Electronic diary (sign and symptoms) during part 1 and 2.
Optional pharmacogenetic research (10 ml blood).

Contacts

Public
Novartis

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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)

Inclusion criteria

* Male or female patients at least 2 years of age. Patients >28 days but <2 years old with bodyweight *3.75 kg at the time of the screening visit will be enrolled in the open label arm only.
* Confirmed diagnosis of TRAPS, HIDS or crFMF at screening.
* Active flare of TRAPS, HIDS or crFMF as evidenced by *mild*, *moderate* or *severe* disease activity (Physician*s Global Assessment of Disease Activity *2) at randomization.
* CRP >10mg/L (normal CRP range *10 mg/L) at randomization.

Exclusion criteria

* Use of the following therapies (within varying protocol defined timeframes, see also protocol page 28-29): Corticosteroids, anakinra, canakinumab, rilonacept, tocilizumab, TNF inhibitors, abatacept, tofacitinib, rituximab, leflunomide, thalidomide, cyclosporine, intravenous immunoglobulin, 6-merceptopurine, azathioprine, cyclophosphamide, or chlorambucil, , any other investigational biologics
* Significant medical diseases, including but not limited to the following:
a) History of organ transplantation
b) Elevated ALT *3x ULN
c) Elevated AST *3x ULN
d) Increase in total bilirubin CTC Grade *2

e) Serious hepatic disorder (Child-Pugh scores B or C)
f) Chronic Kidney Disease NKF stages *4
g) Thyroid disease
h) Diagnosis of active peptic ulcer disease
i) Coagulopathy
j) Significant CNS effects including vertigo and dizziness
* Any conditions or significant medical problems which immunocompromise the patient and/ or places the patient at unacceptable risk for immunomodulatory therapy, e.g.
a) Absolute neutrophil count decreased as per CTC Grade *1
b) Thrombocytopenia CTC * Grade 1
c) Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection
d) HIV, Hepatitis B or C
e) Tuberculosis
f) Requirement for administration of antibiotics against latent TB
g) Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty*s syndrome
* Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose

Study design

Design

Study phase:	3
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):	22-10-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ilaris
Generic name:	canakinumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-07-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2015
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
Other	Clinicaltrials.gov; NCT02059291
EudraCT	EUCTR2013□004291□35-NL
CCMO	NL49974.091.14