An Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents, Aged 2 to 17 Years, with Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) Followed by an Extension Phase

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To describe the pharmacokinetic (PK) profile and effectiveness of sarilumab in patients with pcJIA in order to identifythe dose and regimen for continued development in this population.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON46846

Source
ToetsingOnline

Brief title
DRI13925

Condition

- Immune system disorders congenital
- Autoimmune disorders

Synonym
arthritis in children, poly articular juvenile idiopathic arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sanofi

Intervention

Keyword: children, juvenile arthritis, open-label, sarilumab

Outcome measures

Primary outcome

Assessment of PK parameter: maximum serum concentration observed (Cmax)

Assessment of PK parameter: Area under the serum concentration versus time curve calculated using the trapezoidal method during a dose interval (AUC0-t)

Assessment of PK parameter: Concentration observed before treatment administration during repeated dosing (Ctrough)

Secondary outcome

Number of patients with adverse events

Number of patients with local site reactions

Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology 30 (ACR30) response rate

Change from baseline in individual JIA ACR components

Changes in IL-6 associated biomarkers

Study description

Background summary

Interleukin 6 (IL-6) is a key cytokine involved in the pathogenesis of rheumatoid arthritis (RA) and JIA causing inflammation and joint destruction. The relevance of elevated IL-6 levels to disease mechanisms of polyarticular JIA (RF- and RF+ has been well documented in the medical-scientific literature. Inhibition of IL-6 signaling through blockade of the IL-6 receptor (IL-6R) was first demonstrated to be effective in pcJIA by tocilizumab, an intravenously administered, humanized monoclonal antibody (mAb) to the IL-6R. In the pcJIA studies that led to the approval of tocilizumab in this indication, the safety profile of tocilizumab appeared to be similar to that of the adult RA population.

Sarilumab is a recombinant human monoclonal antibody blocking the IL-6 receptor, that can be administered via subcutaneous injections in stead of IV.

Sarilumab may become an effective and safe therapeutic option for patients suffering from pcJIA. In previous trials in adults with rheumatoid arthritis a significant decease in inflammation was observed. This study will evaluate the efficacy, safety and PK, PD profiles of different doses of sarilumab administered to juvenile patients with pcJIA.

Study objective

To describe the pharmacokinetic (PK) profile and effectiveness of sarilumab in patients with pcJIA in order to identify
the dose and regimen for continued development in this population.

Study design

An Open-label, Ascending, Repeated Dose-finding Study in children aged 2 to 18 years old with pc JIA.

Children are classified in weight groups (10 to 30 kg and 30 to 60 kg), en the heaviest group will start first with the lowest sarilumab dose for a period of 12 weeks. After 6 weeks the cohort is evaluated by the DMC and a second cohort will be opened is the DMC has no objections. Sarilumab is administered every 2 weeks or weekly by subcutaneous injections.

After 12 weeks the patients are offered an extension part of 144 weeks, in case there are no safety issues or benefit issues. The dose of the core study part is maintained.

Intervention

Participants will receive one of three ascending doses of sarilumab trough subcutaeous injection based on body weight [Group A (>=30 kg and <=60 kg) or Group B (<30 kg and >=10 kg)] weekly or biweekly.

Study burden and risks

Based on the safety profile of tocilizumab (an approved IL-6 receptor inhibitor) and other biological DMARDs, potential important risks to be considered with sarilumab administration are tuberculosis and clinically significant opportunistic infections, complications of diverticulitis/gastrointestinal perforations, anaphylaxis, clinical consequences of immunogenicity, clinical consequences of thrombocytopenia, malignancy, and demyelinating disorders. In addition, clinical consequences of laboratory abnormalities which may occur due to sarilumab administration (eg, serious infection secondary to neutropenia) are considered an important potential risk.

Based on the experience to date from the sarilumab clinical development program, the potential important risks associated with sarilumab administration are non-opportunistic infections, neutropenia, elevation in lipids, elevation in liver transaminase, and injection site reactions (ie, erythema, pain).
From the results of the completed studies within the sarilumab RA development program in adult patients, the two selected doses of sarilumab for the phase 3 program appear to be efficacious and have an acceptable safety profile and may serve as an appropriate reference for the further evaluation of sarilumab in pediatric patients with polyarticular course juvenile idiopathic arthritis (pcJIA).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Patients need to fulfill all inclusion criteria mentioned below:;1) -Male and female patients aged >=2 and <=17 years at the time of the screening visit.;2) -Diagnosis of rheumatoid factor-negative or rheumatoid factor positive polyarticular Juvenile Idiopathic Arhtritis (JIA) subtype or oligoarticular extended JIA subtype according to the International League of Associations for Rheumatology (ILAR) 2001 Juvenile Idiopathic Arthritis Classification Criteria with at least 5 active joints as per American College of Rheumatology (ACR) definition for *active arthritis* at screening.;3) -Patient with an inadequate response to current treatment and considered as a candidate for a biologic disease-modifying antirheumatic drug (DMARD) as per Investigator*s judgment.

Exclusion criteria

-Body weight <10 kg or >60 kg.
-If non-steroidal anti-inflammatory drugs taken, dose stable for less than 2 weeks prior to the baseline visit and/or dosing prescribed outside of approved label.
-If non-biologic DMARD taken, dose stable for less than 6 weeks prior to the baseline visit or at a dose exceeding the recommended dose as per local labeling.
-If oral glucocorticoid taken, dose exceeding equivalent prednisone dose 0.5 mg/kg/day (or 30 mg/day) within 2 weeks prior to baseline.
-Prior treatment with anti-interleukin 6 (IL-6) or IL-6 receptor (IL-6R) antagonist therapies, including but not limited to tocilizumab or sarilumab.
-Treatment with any biologic DMARD within 5 half-lives prior to the first dose of sarilumab
-Treatment with a Janus kinase inhibitor within 4 weeks prior to the first dose of sarilumab
-Treatment with any investigational biologic or non-biologic product within 8 weeks or 5 half-lives prior to baseline, whichever is longer.
-Exclusion criteria related to past or current infection other than tuberculosis.

-Any live, attenuated vaccine within 4 weeks prior to the baseline, such as varicella-zoster, oral polio, rubella vaccines;-Wheelchair-bound or bed ridden
- Diagnosis of JIA subtypes except polyarticular RF positive (RF+) or RF negative (RF) JIA or extended oJIA
-Use of parenteral or intra-articular glucocorticoid injection within 4 weeks prior to Baseline
-Lipid-lowering drug stable for less than 6 weeks prior to screening.
-Exclusion related to tuberculosis (TB)
-Prior or current history of malignancy
-Prior or current history of other significant concomitant illness(es) that, according to the investigator*s judgment, would adversely affect the patient*s participation in the study.
-Patient with nonhealed/healing skin ulcers
-Surgery within 4 weeks prior to the screening visit or planned surgery during the course of the study.
- History of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug and known hypersensitivity to any constituent of the product
-History of inflammatory bowel disease, severe diverticulitis, or previous gastrointestinal perforation whatever the cause
-Uncontrolled diabetes mellitus, defined as glycosylated hemoglobin (HbA1c) >=9% at the Screening visit

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2017
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	unknown
Generic name:	sarilumab

Ethics review

Approved WMO Date:	01-06-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-09-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-08-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-05-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2015-003999-79-NL
CCMO	NL57013.041.16

Study results

Date completed:	16-12-2019
Actual enrolment:	1

Summary results
Trial ended prematurely