An Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents, Aged 1 to 17 Years, with Systemic Juvenile Idiopathic Arthritis (sJIA), Followed by an Extension Phase

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

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

Summary

ID

NL-OMON46993

Source
ToetsingOnline

Brief title
DRI13926

Condition

- Immune system disorders congenital
- Autoimmune disorders

Synonym
arthritis in children, systemic 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 (AUCO-t)

Assessment of PK parameter: Concentration observed before treatment

administration during repeated dosing (Ctrough)

Secondary outcome

Number of patients witha dverse 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 systemic 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 sJIA by tocilizumab, an intravenously administered, humanized monoclonal antibody (mAb) to the IL-6R. In the sJIA 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.

Sarilumab may become an effective and safe therapeutic option for patients suffering from sJIA. Th is study will evaluate the efficacy, safety and PK, PO profiles of different doses of sarilumab administered to patients with sJIA.

Study objective

To describe the pharmacokinetic (PK) profile and effectiveness of sarilumab in patients with sJIA 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 1 to 18 years old with sJIA.

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 if 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 subcutaneous injection based on body weight
-Group A (above 30 kg and below 60 kg) or;
-Group B { below 30 kg and above 10 kg)] weekly or biweekly injections

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 ofthe 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 pediatrie patients with polyarticular course juvenile idiopathic arthritis (sJIA).

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

1) Male and female patients aged >=1 and <=17 years at the time of the screening visit.
2) Diagnosis of systemic Juvenile Idiopathic Arthritis (JIA) subtype according to the International League of Associations for Rheumatology (ILAR) 2001 Juvenile Idiopathic Arthritis Classification Criteria with the following features at screening: ->=5 active joints at screening or; ->=2 active joints at screening with systemic JIA fever bigger as 37.5 °C in the 3 days preceding baseline or for at least 3 out of any 7 consecutive days during screening despite glucocorticoids at a stable dose for at least 3 days.
3) Patients with an inadequate response to current treatment and considered as a candidate for a biologic disease-modifying anti-rheumatic drug (DMARD) as per Investigator*s judgment.

Exclusion criteria

-Body weight below 10 kg or more than 60 kg.
-Uncontrolled severe systemic symptoms and/or Macrophage Activation Syndrome within 6 months prior to screening.
-If nonsteroidal anti-inflammatory drugs [NSAIDs, including cyclo-oxygenase-2 inhibitors (COX-2)] 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 1 mg/kg/day (or 60 mg/day) within 3 days prior

to baseline.
-Use of parenteral intra-articular injection of glucocorticoid within 4 weeks prior baseline.
-Lipid-lowering drug stable for less than 6 weeks prior to screening.
-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 treatment for sJIA 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 related to tuberculosis (TB)
-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. Killed or inactive vaccine may be permitted based on the Investigators judgment.
-Severe cardiac disease due to sJIA.
-History of or ongoing interstitial lung disease, pulmonary hypertension, pulmonary alveolar proteinosis.

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):	31-05-2018
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	not known yet
Generic name:	sarilumab

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-04-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2018
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	04-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-09-2019
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	EUCTR2015-004000-35-NL
CCMO	NL59322.041.16
Other	U1111-1177-3584