EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF TOFACITINIB FOR TREATMENT OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (sJIA) WITH ACTIVE SYSTEMIC FEATURES IN CHILDREN AND ADOLESCENT SUBJECTS

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Primary:* To assess the sustained efficacy of tofacitinib versus placebo in sJIA patients, as measured by time to sJIA flare in the double-blind randomized withdrawal phase.Secondary:* To assess efficacy of tofacitinib versus placebo in sJIA...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON51984

Source
ToetsingOnline

Brief title
A3921165

Condition

- Autoimmune disorders
- Joint disorders

Synonym
juvenile rheumatoid arthritis, Still's disease

Research involving
Human

Sponsors and support

Primary sponsor: Syneos Health Netherlands B.V
Source(s) of monetary or material Support: Industry

Intervention

Keyword: arthritis, Children, sJIA, Still's disease

Outcome measures

Primary outcome

* Time to sJIA disease flare in the double-blind randomized withdrawal phase.

Secondary outcome

Efficacy endpoints:

* Occurrence of disease flares in the double-blind phase at each visit.

* Achievement of corticosteroid tapering per protocol at the end of the

open-label active treatment period in applicable subjects receiving

corticosteroids on study Day 1 of the open-label phase.

* Achievement of a corticosteroid dose of <=0.2 mg/kg/day or 10 mg/day

(whichever is lower) at the end of the open-label treatment period in subjects

receiving corticosteroids on Day 1 of the open-label phase.

* Adapted sJIA ACR 30/50/70/90/100 response at every visit from Day 7 onward in

the open-label and double-blind phase.

* Fever (Temp >38 Degrees Celsius) attributed to sJIA at Day 3, Day 7 and Day

14 of the open-label phase.

* CRP <=10 mg/L at every visit of the open-label phase.

* *Absence of fever*, defined as absence of fever due to sJIA in the week

preceding the assessment at every visit from Day 7 onward in the open-label and double-blind phase.

* Time to first Adapted JIA ACR 30 response in Part 1 of the open-label phase.

* Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS 27) at every visit from Day 7 onward in the open-label and double-blind phase.

* Change from baseline in each JIA ACR core variable at every visit from Day 7 onward in the open-label and double-blind phase.

* Change from baseline in Child Health Questionnaire (CHQ) responses at the end of Part 1 and Part 2 of the open-label phase, at randomization and every 6 months thereafter.

* Change from baseline in Child Health Assessment Questionnaire (CHAQ) at every visit from Day 7 onward in the open-label and double-blind phase.

* Occurrence of inactive disease status and minimal disease activity at every visit from Day 7 onward (JADAS-27) in the open-label and double-blind phase.

* Occurrence of inactive disease status and clinical remission at every visit from Day 7 onward (JIA ACR) in the open-label and double-blind phase.

Exploratory

* Change from baseline in various genomic and serum biomarkers following treatment with tofacitinib.

Safety Endpoints

* All adverse events (AEs), including Serious Adverse Events (SAEs).

* Macrophage activation syndrome (MAS) events.

* Serious infections, including tuberculosis, varicella and herpes zoster and opportunistic infections.

* Clinically significant abnormal laboratory parameters, including abnormal hematology parameters, lipid parameter changes, liver enzymes, serum creatinine elevation.

* Malignancies, including lymphoma and non-melanoma skin cancer.

* Gastrointestinal perforations.

* Cardiovascular diseases.

* Assessments of growth and pubertal development.

Study description

Background summary

The safety and effectiveness of tofacitinib for the treatment of rheumatoid arthritis (RA) has been demonstrated in adult subjects. The Sponsor is conducting a pediatric investigational program to determine the safety and efficacy of tofacitinib in subjects 2 to <18 years of age for the treatment of Juvenile Idiopathic Arthritis (JIA). As part of this pediatric investigational program, study A3921165 will evaluate efficacy, safety, tolerability and pharmacokinetics of tofacitinib as treatment for systemic (s)JIA. In this study, after 12 to 40 weeks of treatment with open-label tofacitinib, sJIA patients who are able to taper corticosteroids (CS) while maintaining an Adapted JIA ACR 30 response will be identified as *responders*. These responders will proceed to a double-blind withdrawal phase in which they will be randomized to either continue with tofacitinib treatment or start placebo treatment. Sustained efficacy of tofacitinib to prevent disease flare will be evaluated in the randomized withdrawal phase.
It is expected that Tofacitinib will demonstrate a reduction in signs and symptoms of sJIA compared to placebo.

Study objective

Primary:
* To assess the sustained efficacy of tofacitinib versus placebo in sJIA patients, as measured by time to sJIA flare in the double-blind randomized

withdrawal phase.

Secondary:
* To assess efficacy of tofacitinib versus placebo in sJIA patients at various time points in the double-blind randomized withdrawal phase, as measured by:
a. Percentage of subjects with sJIA disease flares;
b. Percentage of subjects with Adapted JIA ACR 30/50/70/90/100 responses;
c. Changes from baseline in Juvenile Arthritis Disease Activity Score (JADAS-27);
d. Percentage of subjects achieving inactive disease and clinical remission (JIA ACR);
e. Percentage of subjects with inactive disease and minimal disease activity (JADAS-27);
f. Other evaluations specified under *Efficacy endpoints* for the double-blind phase.
* To assess the efficacy of tofacitinib in sJIA patients in the open-label treatment phase,
as measured by:
a. Percentage of subjects with successful corticosteroids tapering per protocol at the end of the open-label phase in subjects with sJIA receiving corticosteroids at start of open-label phase;
b. Percentage of subjects with Adapted JIA ACR 30/50/70/90/100 responses at every visit from Day 7 onward;
c. Other evaluations specified under *Efficacy endpoints* for the open-label phase.
* To assess the safety and tolerability of tofacitinib in sJIA patients.
* To assess the pharmacokinetics of tofacitinib in sJIA patients in the open-label phase.

Exploratory Objective
* To evaluate exploratory biomarker and genomic samples to characterize the effect of
tofacitinib.

Study design

This is a 2-phase randomized withdrawal study to evaluate efficacy, safety and tolerability, and pharmacokinetics of tofacitinib as a treatment for sJIA.
The first phase will be open-label were all subjects receive tofacitinib. The second phase will be double-blind placebo controlled.

Intervention

Open-label phase: All subjects <40 kg will receive tofacitinib 5 mg BID oral tablets, and all subjects <40 kg will receive a weight-based lower dose of tofacitinib oral solution (1 mg/mL) BID. Each dose must be taken two times per

day, about 12 hours apart

Double-blind phase: Eligible subjects will be randomized in a 1:1 ratio to either continue on the same dose of tofacitinib that they received in the open-label phase or start placebo.

Study burden and risks

The patients will need to do/undergo the following for the study:
-Visit the hospital 16 times
- 22 times blood tests
-Urine test
-Physical exam, vital signs, demographic and medical history
-Pregnancy tests in women of childbearing potential
-An X-ray only if required to determine tuberculosis
-examination of the joints
-questions about pain and stiffness
-questions about possible immobilization, surgery or heart conditions
-Female patients: no breastfeeding allowed. Effective methods of birth control must be used from the time of signing the ICF, throughout the entire study and for X days following the last dose of the study drug.
Male patients: due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and continuing for at least x days following the last dose of study drug.
-Parents of the patients will be asked to complete a questionnaire about their child's condition

The nature and degree of the risk varies with the patient population; however, these potentially important risks include lipid elevations, decreases in hemoglobin, decreases in neutrophil and lymphocyte counts, increases in serum creatinine, increases in serum creatine kinase, infection risk, lymphoproliferative disorder/lymphoma risk, malignancy risk, non-melanoma skin cancer, gastrointestinal perforations, viral reactivation, including herpes zoster, tuberculosis, transaminase elevations, drug hypersensitivity and effects on pregnancy and the fetus. Additionally, venous thromboembolism (VTE) has been identified as an important identified risk associated with tofacitinib. Safety assessments, including physical examinations, clinical laboratory tests, adverse event monitoring vital signs and VTE risk assessment will be performed in Study A3921165. Safety assessments, inclusion/exclusion criteria, monitoring and discontinuation criteria including newly added criteria for the discontinuation of a subject with a VTE event were designed to manage and mitigate the safety risks associated with tofacitinib therapy.
Based on the totality of the data, the sponsor is of the opinion that the overall risk-benefit assessment for this study is favorable for children with sJIA. Thorough safety monitoring and staggering of cohorts based on age for index studies will be used to minimize risk in the pediatric population.

Contacts

Public
Syneos Health Netherlands B.V

De Entrée 99-197
Amsterdam 1101 HE
NL
Scientific
Syneos Health Netherlands B.V

De Entrée 99-197
Amsterdam 1101 HE
NL

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 or female aged 2 to < 18 years.
2.Diagnosed with sJIA according to International League Against Rheumatism (ILAR) criteria, and, in the opinion of the investigator, prior to screening. Subjects with first-degree relatives with history of psoriasis, ankylosing spondylitis, enthesis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis may be allowed for enrollment after consultation with the sponsor. Subjects must have active disease at the time of enrollment defined as:
a.Documented intermittently spiking temperature >38*C for at least 1 day due to sJIA in the screening period and within 1 week before the first dose, and the presence of at least 2 joints with active arthritis at screening and baseline,

and an ESR >30 mm/hr [1.5 X ULN] at screening.
OR
b.Only after cohort review is completed and enrollment is opened without restrictions at a particular dose level: The presence of at least 5 joints with active arthritis at screening and baseline, and an ESR >30 mm/hr [1.5 X ULN] at screening. Refer to Section 3.4 of the protocol for details.
3.Treatment with stable doses of methotrexate (MTX) and/or oral CSs is permitted:
•For subjects taking MTX: Treatment for >=3 months with MTX and with a stable dose of MTX (dose must be <=25 mg/wk or <=20 mg/m2/week, whichever is lower) for at least 46 weeks before the first study drug dose (Day 1). Subjects taking MTX must be taking folic acid or folinic acid in accordance with local standards.
•For subjects taking CS: Treatment with a stable dose of oral prednisone (<=1 mg/kg/day up to a maximum of 30 mg/day), or equivalent, for at least 1 week before the first study drug dose (Day 1).
4.No evidence or history of untreated or inadequately treated active or latent tuberculosis (TB) infection as evidenced by the following:
•A negative QuantiFERON® TB Gold or Glod Plus In Tube test performed within the 3 months prior to screening. A negative purified protein derivative (PPD) test can be substituted for the QuantiFERON® TB Gold or Gold Plus In Tube test only if the central laboratory is unable to perform the test or cannot determine the results to be positive or negative and the Pfizer medical monitor is informed and agrees on a case by case basis.
•Chest radiograph without changes suggestive of active tuberculosis (TB) infection within 3 months prior to screening is recommended and should be performed according to local standards of care or country specific guidelines.
•No history of either untreated or inadequately treated latent or active TB infection.
5.Fertile males and females who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must be willing and able to use a highly effective method of contraception as outlined in this protocol during the study and for at least 28 days after the last dose of study medication (see Section 4.4.1 of the protocol).
Country-specific amendment for EU sites (including UK): Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined below) throughout the study and for at least 28 days (90 days for male subjects) after the last dose of study drug where there is known or suspected teratogenicity. (see Section 4.4.1 of the protocol).
6.Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
7.Evidence of a personally signed and dated Informed Consent document and Assent document (as appropriate) indicating that the subject and a legally acceptable representative/parent/legal guardian has been informed of all

pertinent aspects of the study.

Exclusion criteria

Subjects with any of the following characteristics/conditions will not be included in the study:
1.Previous JIA treatment with tofacitinib.
2.Current symptoms or findings of myocarditis, endocarditis or more than minimal pericardial effusion associated with sJIA.
3.Current symptoms or findings of more than minimal pleuritis with sJIA.
4.Subjects who are still within the washout periods for disallowed nonbiological and biological DMARDs as indicated in Section 5.8.1.2 of the protocol.
5.Infections:
a.Chronic infections;
b.Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 3 months prior to the first dose of study drug;
c.Any treated infections within 2 weeks of baseline;
d.A subject known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C (see Section 7.2.8 of the protocol);
e.History of infected joint prosthesis with prosthesis still in situ.
6.History of recurrent (more than one episode) herpes zoster or disseminated (at least one episode) herpes zoster, or disseminated (at least one episode) herpes simplex.
7.Diagnosis of active Macrophage Activation Syndrome (MAS) within 3 months prior to the first dose of study drug.
8.Blood dyscrasias, including (see Appendix 7 of the protocol):
a.Hemoglobin < 9 g/dL;
b.White Blood Cell count < 3.0 x 109/L;
c.Absolute Neutrophil count < 1.2 x 109/L;
d.Platelet count < 100 x 109/L;
e.Absolute Lymphocyte count < 0.75 x 109/L.
9.Estimated glomerular filtration rate [GFR] < 40 mL/min/1.73 m2 at Screening. GFR will be calculated by the central lab using the bedside Schwartz formula (see Appendix 4 of the protocol).
10.Current or recent history of uncontrolled clinically significant renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiac or neurologic disease.
11.Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >=1.5 times the upper limit of normal or any other clinically significant laboratory abnormality (see Appendix 7 of the protocol).
12.History of any other rheumatologic disease, other than Sjogren*s syndrome.
13.History or current symptoms suggestive of lymphoproliferative disorders (eg, Epstein Barr Virus [EBV] related lymphoproliferative disorder, lymphoma,

leukemia, or signs and symptoms suggestive of current lymphatic disease).
14.Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of study drug, or is expected to be vaccinated or there are household members that require oral polio vaccination (see Section 4.5.2 Vaccination in Household Members) during treatment or during the 6 weeks following discontinuation of study drug.
15.Current malignancy or history of any malignancy with the exception of adequately treated or excised basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ.
16.Subjects with a first degree relative with a hereditary immunodeficiency; IgA deficiency not exclusionary.
17.Recent (within 28 days prior to first dose of study drug) significant trauma or major surgery.
18.Subjects receiving potent and moderate CYP3A4 inhibitors or inducers (Appendix 5 of the protocol).
19.Prior treatment with non B cell specific lymphocyte depleting agents/therapies (eg, almetuzumab [CAMPATH®], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc.). Subjects who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal CD 19/20+ counts by FACS analysis.
20.Use of prohibited prescription or non prescription drugs and dietary supplements listed in Appendix 1 and Appendix 5 of the protocol within the specified time frame prior to the first dose of study medication.
21.Herbal supplements, unless discontinued at least 28 days prior to the first dose of study medication.
22.Subjects who are children of or related to investigational site staff members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study.
To see the full list of exclusion criteria see paragraph 4.2. Exclusion Criteria of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Xeljanz
Generic name:	Tofacitinib citrate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-12-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-10-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-05-2022

Application type:	Amendment
Review commission:	METC NedMec
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Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-11-2022
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	EUCTR2017-002018-29-NL
CCMO	NL75258.041.20