A LONG-TERM, OPEN-LABEL FOLLOW-UP STUDY OF TOFACITINIB FOR TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Primary* The primary objective of this study is to determine the long term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA.Secondary* The secondary objective of this study is to evaluate the persistence of...

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

Summary

ID

NL-OMON52164

Source
ToetsingOnline

Brief title
A3921145

Condition

- Autoimmune disorders
- Joint disorders

Synonym
joint inflammation, Juvenile arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Industry

Intervention

Keyword: arthritis, children, JIA, Long-term

Outcome measures

Primary outcome

Primary

* Standard laboratory safety data and adverse event (AE) reports. Body weight, height and Tanner stages will be collected to assess growth and physical development.

Secondary outcome

Secondary

The following efficacy parameters will be assessed:

* Physician global evaluation of disease activity at each visit.

* Number of joints with active arthritis at each visit.

* Number of joints with limitation of motion at each visit.

* Index of inflammation (C-reactive protein [CRP] and Erythrocyte Sedimentation Rate [ESR]) at each visit.

* Childhood Health Assessment Questionnaire (CHAQ) at each visit.

* Parent*s Assessment of Physical Function (CHAQ Disability Index).

* Parent*s Assessment of Child*s Arthritis Pain (CHAQ Discomfort Index, Visual Analog Scale [VAS]).

* Parent*s Global Assessment of Overall Wellbeing (CHAQ subsection, Visual Analog Scale [VAS]).

* JIA American College of Rheumatology (ACR) response and occurrence of JIA ACR disease flare at each visit.

* JIA ACR Clinical Inactive Disease status and Clinical Remission on Medication at each visit.

* Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 27-CRP and JADAS 27-ESR, and occurrence of JADAS minimum disease activity and inactive disease at each visit.

* Eligibility of tapering defined per protocol for corticosteroids, MTX/leflunomide, and tofacitinib.

* In subjects with sJIA: *Absence of Fever*, defined as absence of fever due to sJIA in the week preceding the assessment at each visit.

* In subjects with Enthesitis Related Arthritis (ERA): Change from baseline in the Tender Entheseal Assessment, Modified Schober*s Test, Overall Back Pain and Nocturnal Back Pain responses at various visits.

* In subjects with psoriatic arthritis (PsA): Change from baseline in body surface area (BSA) affected by psoriasis and Physician*s Global Assessment (PGA) of psoriasis) at various visits.

Exploratory

* Plasma concentration time data for tofacitinib will be analyzed to characterize the PK in this subject population. Exposure-response relationship will be explored for various efficacy and safety endpoints after long-term exposure of tofacitinib.

Study description

Background summary

Tofacitinib is a potent, selective inhibitor of the Janus Kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, to a lesser extent Tyrosine Kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukins (IL) IL-2, -4,-7,-9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN) *. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.
Tofacitinib pediatric development program is designed to demonstrate both efficacy, as demonstrated by a reduction in signs and symptoms of Juvenile Idiopathic Arthritis (JIA) in subjects 2 years of age and older, and safety supporting the use of tofacitinib for the treatment of pediatric subjects with JIA. The rationale of this study is to enable subjects potentially benefitting from treatment in a previous qualifying/index study to continue to receive tofacitinib at the same dose as the qualifying/index study (unless further analysis of the qualifying/index study data indicate otherwise), and to characterize long-term safety and tolerability of tofacitinib for the treatment of JIA.

Study objective

Primary
* The primary objective of this study is to determine the long term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA.

Secondary
* The secondary objective of this study is to evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.

Exploratory
The exploratory objectives of this study are:
* To assess tofacitinib pharmacokinetics (PK) in pediatric subjects on a stable dose of tofacitinib in the setting of a long-term, open label study.
* To assess changes in PK parameters (within subject) with increase in weight in this pediatric population and to explore exposure-response relationships of tofacitinib for various efficacy and safety endpoints after long-term exposure

of tofacitinib in this pediatric population.

Study design

A long-term open-label follow-up study

Intervention

Oral solution (1 mg/mL concentration) will be used for subjects weighing <40 kg. Oral tablets (5 mg) will be used for subjects weighing * 40 kg; subjects who are unable to swallow
tablets will have the option of taking oral solution

Study burden and risks

Patients are expect to visit the hospital around 4-5 times a year. The following procedures will happen:
-Blood an urine tests (including HIV, Hepatitis B, Hepatitis C, Tuberculosis)
-Physical exam, either brief or a complete exam, vital signs
-Pregnancy tests in women of childbearing potential
-examination of the joints
-questions about:
-any changes in the subjects health since last visit
-medications and any symptoms since last visit
-pain and stiffness
-possible immobilization, surgery or heart conditions
-Uveitis exam
-Fasting 9-12 hours before some visits (every 6 months the first 5 years, every year after that)
-questionnaire for the parents to complete on 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 eventmonitoring, vital signs and VTE risk assessment will be performed in Study A3921145. 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 JIA. Thorough safety monitoring and staggering of cohorts based on age for index studies will be used to minimize risk in the pediatric population.

Contacts

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Pfizer

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US
Scientific
Pfizer

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New York NY 10017
US

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)

Inclusion criteria

Subjects eligibility should be reviewed and documented by an appropriately investigator before subjects are included in the study. All subjects must meet Inclusion Criteria 1-11 to be eligible for enrollment into the study: 1)

Pediatric subjects with JIA aged from 2 to less than 18 years who met entry criteria for the qualifying/index study and in the opinion of the investigator have sufficient evidence of JIA disease activity to warrant use of tofacitinib as a DMARD. Subjects turning 18 years of age during participation in the qualifying/index study or subsequently will be eligible for participation in this study. 2) The subject has discontinued disallowed concomitant medications for the required time prior to the first dose of study drug, as defined in Appendix 1, and is taking only those concomitant medications in doses and frequencies allowed by the protocol. 3) Fertile male subjects and female subjects of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must be using a highly effective method of contraception as outlined in this protocol throughout the study and for at least 28 days after the last dose of study medication. 4) Subjects must have previously completed participation in a qualifying study of tofacitinib for the treatment of JIA. Subjects who have required earlier discontinuation of treatment in a qualifying study for reasons other than tofacitinib related serious adverse events may be eligible. 5) For subjects receiving methotrexate (MTX) treatment, MTX may be administered either orally or parenterally at doses not to exceed 25mg/week or 20 mg/m2/week, whichever is lower. Subjects taking methotrexate must be taking folic acid or folinic acid in accordance with local standards. 6)For subjects receiving an oral glucocorticoid, glucocorticoids may be administered at a maximum dose of 0.20 mg/kg/day or 10 mg/day, prednisone or equivalent, whichever is lower. 7)For subjects receiving leflunomide treatment, leflunomide may be administered according to the following dosing scheme:10 mg every other day for subjects patients weighing less than 20 kg; 10 mg every day for subjects weighing between 20 and 40 kg,; 20 mg every day for subjects weighing over 40 kg; Or as according to local standards. 8)For subjects receiving sulfasalazine, chloroquine, or hydroxychloroquine treatment, these medications may be administered according to local standards. 9)Evidence of a personally signed and dated informed consent document with assent as appropriate indicating that the subject (or a legally acceptable representative/ parent(s)/legal guardian) has been informed of all pertinent aspects of the study. 10)Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures. 11)Subjects for whom, in the Investigator*s opinion, treatment with tofacitinib is considered clinically appropriate while also taking into consideration currently available therapies and prior response to these therapies. Subjects who enroll outside the 14 day window of the EOS Visit of their qualifying/index study must also meet Inclusion Criterion 12 to be eligible for enrollment into the study: 12) No evidence of active tuberculosis (TB) or inadequately treated tuberculosis (TB) infection (active or latent) as evidenced by all of the following: a) A negative QuantiFERONÒ-TB Gold In-Tube test4 performed within the 3 months prior to screening. A negative purified protein derivative (PPD) test with a result of <5 mm induration can be substituted for the QuantiFERONÒ-TB Gold 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 approves it, on a case-by-case basis. b) 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. c) No history of either untreated or inadequately treated latent or active TB infection. If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a PPD test nor a QuantiFERON- Gold®TM test need be obtained. A chest radiograph should be obtained if not done within the 3 months prior to screening. To be considered eligible for the study, the chest radiograph must be negative for active tuberculosis infection. A subject who is currently being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection (<5%), documentation of an adequate treatment regimen, and prior approval of the Sponsor.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study: For subjects who enroll outside the 14 day window of the EOS Visit of their qualifying/index study (Exclusion 1-3):
1) Blood dyscrasas, including: a. Hgb < 10 g/dL or Hct <33%. b. WBC <3.0 x 109/L. c. Neutrophil count <1.2 x 109/L. d. Platelet count <100 x 109/L. e. Lymphocyte count of <0.75 x 109/L. 2) Estimated glomerular filtration rate [GFR] <40 mL/min/1.73 m2 calculated using Bedside Schwartz formula (Appendix 5) at the Screening Visit. 3) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) *1.5 times the upper limit of normal or any other clinically significant laboratory abnormality. For all subjects: 4) Persistent oligoarthritis, and undifferentiated JIA. 5) Current or recent history of uncontrolled clinically significant renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, or neurological disease. 6) History of any other rheumatic autoimmune disease, other than Sjogren*s syndrome. 7) History or current symptoms suggestive of any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease. 8) Infections: a) Chronic infections. b) Any infection requiring hospitalization, parenteral antimicrobial therapy or judged to be opportunistic by the investigator within the 6 months prior to the first dose of study drug: c) Any treated infections within 2 weeks of baseline visit. (excluding those treated with topicals only) d) A subject known to be infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C virus. e) History of infected joint prosthesis with prosthesis still in situ.
9) History of recurrent (more than one episode) herpes zoster or a single episode of disseminated herpes zoster or a single episode of disseminated

(both oral and gential lesions simutaneously, or widespread lesions not contaminaed to oral or gential regions alone) herpes simplex. 10) Previously failed treatment with another JAK inhibitor, such as baricitinib. 11) Subjects taking potent and moderate cytochrome P450 3A4 (CYP3A4) inhibitors (Appendix 6). 12) Subjects taking potent and moderate CYP3A4 inducers (Appendix 6).13) Participation in studies of investigational compounds (excluding qualifying/index study with tofacitinib) within 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug. Subjects cannot participate in studies of other investigational compounds at any time during their participation in this study. Exposure to investigational biologics should be discussed with the Pfizer Medical Monitor. 14) Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies [eg. almetuzumab (CAMPATHÒ), 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. 15) Pregnant or nursing females are excluded. 16) Intramuscular or intravenous corticosteroids in the 4 weeks preceding first dose of study medication (oral corticosteriods permitted as per inlcusion criterion). 17) Subjects who have been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication. All study participants should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry). (See Life Style Guidelines for further information regarding avoidance of household contacts who may be vaccinated). 18) Use of prohibited prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication. 19) Herbal supplements must be discontinued at least 4 weeks prior to the first dose of study medication. 20) Subjects with a first degree relative with a hereditary immunodeficiency; IgA deficiency not exclusionary. 21) Subjects with a malignancy or with a history of malignancy wi

th the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ. 22) Recent (within 28 days prior to first dose of study drug) significant trauma or major surgery. 23) Unwilling or unable to comply with the Life Style Guidelines described in this protocol. Please see the Protocol Section 4.2 Exclusion Criteria for additional exclusion criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
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:	05-02-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	26-07-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2022
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	EUCTR2011-004915-22-NL
ClinicalTrials.gov	NCT01513902
CCMO	NL76027.041.21