Biologika in der Kinderrheumatologie-Register/
(Biologics in Paediatric Rheumatology-Registry)

BiKeR-Registry
Author : 
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Registry Protocol
prospective non interventional epidemiological survey

CONFIDENTIAL

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## 2. Synopsis

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<th>Biologika in der Kinderrheumatologie-Register/Biologics in Paediatric Rheumatology-Registry</th>
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<tr>
<td>Study phase</td>
<td>Registry (prospective non interventional study)</td>
</tr>
<tr>
<td>Investigational product</td>
<td>Not applicable. All drugs monitored are approved for the indication. According to approved label of Adalimumab, Etanercept and Tocilizumab</td>
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<tr>
<td>Dosage</td>
<td><strong>Adalimumab</strong>&lt;br&gt;24 mg/sqm s.c. every second week up to 40 mg per injection</td>
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<td><strong>Etanercept</strong>&lt;br&gt;0.4 mg/kg bw s.c. twice weekly up to 25 mg per injection&lt;br&gt;or&lt;br&gt;0.8 mg/kg bw s.c. weekly up to 50 mg per injection</td>
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<td><strong>Tocilizumab</strong>&lt;br&gt;Systemic onset Juvenile Idiopathic Arthritis (so-JIA):&lt;br&gt;Children with so-JIA up to 30 kg: 12 mg/kg body weight i.v. every 2 weeks interval&lt;br&gt;Children with so-JIA over 30 kg body weight: 8 mg/kg body weight i.v. every 2 weeks interval&lt;br&gt;polyarticular juvenile idiopathic arthritis (pJIA):&lt;br&gt;Children with pJIA over 30 kg: 8 mg/kg per dose i.v. every 4 weeks&lt;br&gt;Children with pJIA up to 30 kg: 10 mg/kg per dose i.v. every 4 weeks</td>
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<tr>
<td>Route of administration</td>
<td>According to label&lt;br&gt;Intravenous infusion (i.v.) or subcutaneous injection (s.c)</td>
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<tr>
<td>Indication</td>
<td>Systemic onset Juvenile Idiopathic Arthritis (soJIA), extended oligoarthritis, psoriatic arthritis, enthesitis related arthritis and polyarticular juvenile idiopathic arthritis (pJIA).</td>
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Objectives

**Primary**

- To conduct a long term observational safety and efficacy (clinical response according to the PedACR30/50/70/90/100 criteria, JADAS 10 criteria and proposed criteria for inactive disease and remission) registry of in label treatment with tocilizumab in systemic onset juvenile idiopathic arthritis (so-JIA), extended oligoarthritis (extOA), psoriatic arthritis (PsA), enthesitis related arthritis (ERA) and polyarticular juvenile idiopathic arthritis (pJIA).

**Secondary**

- To assess the long-term efficacy on remission of tocilizumab and the long term efficacy on joint erosion, joint damage and treatment adherence in subjects with so-JIA, extOA, PsA, ERA and pJIA.
- To identify potential predictors of clinical response and remission.
- To assess treatment duration, dosing and reasons for dose modifications.
- To assess changes in co-medications, for examples reduction of corticosteroids.
- To assess patient growth, development and bone density (if routinely available).
- To assess numbers and incidence rates of adverse events (AEs), AEs of special interest and serious AEs (SAEs).
- To assess the occurrence of fractures (fracture rate and location of fractures).
- To assess treatment interruptions and treatment withdrawal due to AEs.
- To compare incidence rates of adverse events (AEs) and serious AEs (SAEs) observed in JIA patients treated with TNF-inhibiting biologics, Non-TNF-inhibiting biologics and JIA patients treated without biologics but with methotrexate (MTX). These MTX treated patients are already followed in a control registry. This will include but will not be limited to the evaluation of the effect on: bone marrow, liver, lung, kidney, neurological, skin and gastrointestinal, serious opportunistic infections, and malignancies.
- To establish different cohorts of children (treated with anti-TNF- biologics ± MTX, Tocilizumab ± MTX, MTX alone, not treated with MTX or biologics) each of which will be used as controls for the others.

Patient population

**Incident patient population**

Male and female patients 2 to <18 years of age with systemic onset juvenile idiopathic arthritis (soJIA) or polyarticular juvenile idiopathic arthritis (pJIA) with an active disease who start treatment with a biologic according to label.

**Prevalent patient population**

Male and female patients 2 to <18 years of age with systemic onset juvenile idiopathic arthritis (soJIA) or polyarticular juvenile idiopathic arthritis (pJIA) who are currently treated with tocilizumab.

Study design

Multi-center, prospective, non-interventional registry

Duration of treatment

- Patients with so-JIA will be followed for at least 5 years and pJIA for at least 10 years.
- Patients who discontinued treatment with biologics will be followed for at least 3 years.
Methodology

so-JIA and pJIA
- Remission criteria described by Wallace et al. including the presence of fever
- PedACR 30/50/70/90/100-criteria
- Modified PedACR-CRP 30/50/70/90/100-criteria
- Physician's global assessment of disease activity
- Parents' global assessment of subject's overall well-being
- CHAQ (Childhood Health Assessment Questionnaire)
- Pediatric Total Joint Assessment, including swollen joint count (SJC), tender joint count (TJC), and limitation of passive motion joint count (LOM)
- Growth patterns (relative to age specific standards for height and weight)
- Developmental patterns (relative to onset of menarche [for females] and pubertal changes)
- Fracture and fracture rate
- Bone density (if available)

pJIA
- Polyarticular juvenile idiopathic arthritis (pJIA), as defined by the International League of Associations of Rheumatology (Petty et al. 2004)
- JADAS-10 to evaluate effectiveness of 10 mg/kg TCZ in pJIA patients weighing <30 kg
- JADAS-10 to evaluate effectiveness of TCZ in patients with RF-positive and RF-negative pJIA

so-JIA
- Fracture and fracture rate
- Bone density (if available)

Number of registry centers | Unlimited (we expect to recruit 70 centers in Germany)
Number of patients | Unrestricted (we expect to recruit at least 200 patients treated with tocilizumab and 200 patients treated with TNF-inhibitors)
Adverse events

All adverse events will be collected during the treatment period.

Adverse Events of special interest are defined as:

- Anaphylaxis/ Hypersensitivity
- Autoimmune diseases
- Bleeding events
- Chronic inflammatory bowel disease
- Cytopenia
- Demyelinating disorders
- Gastrointestinal perforations and related events
- Hepatic events
- Infections (including opportunistic infections)
- Macrophage activation syndrome (MAS)
- Malignancies
- Myocardial infarction/ acute coronary syndrome
- Pregnancy
- Stroke
- Systemic lupus erythematosus
- Thrombotic events
- Tuberculosis
- Uveitis

AEs of special interest are to be processed like SAEs. That means that AEs of special interest must be reported by the investigator within one working day.

Analysis plan

so-JIA and pJIA

- Reports on adverse events (AEs) adverse events of special interest and serious adverse events (SAEs)
- Assessment of the clinical response according to the original PedACR 30/50/70/90/100 criteria and the modified original PedACR-CRP 30/50/70/90/100 criteria
- Assessment of Patient oriented outcome parameters (pain, overall well being, CHAQ, days missing on school, days missing on work)
- Assessment of the remission induction rate
- All analysis will be performed in a descriptive manner

pJIA

- Assessments of JADAS-10 to evaluate effectiveness of 10 mg/kg TCZ in pJIA patients weighing <30 kg
- Assessments of JADAS-10 to evaluate effectiveness of TCZ in patients with RF-positive,RF-negative pJIA and extended oligoarticular JIA separately.
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Planned start of recruitment: 1st quarter of 2015
Planned end of recruitment: A planned end date of recruitment is dependent on the total number of patients required for analysis and is indeterminate with no maximum number of patients.

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4. Investigators and study administrative structure

Coordinating Investigator / Projektleiter

Investigators

Nation wide multi-center observational study open to all contributors willing to participate and to follow the protocol

Emergency Contact

OR

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Asklepios Clinic Sankt Augustin
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Statistics and Biometrican

5. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease in childhood and can lead to severe disability [1,2,3]. The term JIA encompasses a group of clinically heterogeneous arthritides that begin prior to age 16 years, are of unknown cause and present with joint pain, stiffness and swelling that persist for
Other DMARDs such like gold salts, penicillamine, sulfasalazine, the antimalarial drugs hydroxychloroquine and several national treatment guidelines are needed as bridging treatment until DMARD treatment reached their effectiveness. Methotrexate (MTX) has been used for decades despite the lack of controlled trials performed in juvenile arthritides simply because of their methotrexate sometimes are considered while data for these strategies are scarce. Since these drugs have been used for decades despite the lack of controlled trials performed in juvenile arthritides simply because of their efficacy in adult rheumatoid arthritis they will not be discussed in details. Methotrexate and leflunomide as well as sulfasalazine in HLA-B27 associated arthritis are the only exceptions with evidence for the use in juvenile idiopathic arthritis [9,10,11].

Intraarticular corticosteroids and symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) often are sufficient for those JIA patients presenting with few affected joints only. Primary introduction of so called disease modifying antirheumatic drugs (DMARD) is more and more immediately recommended for polyarticular JIA and systemic onset JIA. The use of intraarticular corticosteroids and NSAIDs in these patients may be needed as bridging treatment until DMARD treatment reached their effectiveness. Methotrexate (MTX) has been studied in controlled clinical trials and emerged to be the most common first line DMARD treatment according to several national treatment guidelines [6,7].

Other DMARDs such like gold salts, penicillamine, sulfasalazine, the antimalarial drugs hydroxychloroquine and chloroquine and the immunosuppressants azathioprine and cyclosporin A currently are rarely used for treatment of JIA [8]. Combination treatment using sulfasalazine, anti-malaria drugs or cyclosporin A together with methotrexate sometimes are considered while data for these strategies are scarce. Since these drugs have been used for decades despite the lack of controlled trials performed in juvenile arthritides simply because of their efficacy in adult rheumatoid arthritis they will not be discussed in details. Methotrexate and leflunomide as well as sulfasalazine in HLA-B27 associated arthritis are the only exceptions with evidence for the use in juvenile idiopathic arthritis [9,10,11].

For decades, the primary goal of treatment of JIA has been managing of pain and other inflammatory symptoms combined with physiotherapy. In recent years innovative developments in the pharmacotherapy of JIA enabled not only prevention of long-term damage and disability but also induction of remission as a reachable goal became a real option. Drug therapy should, if possible, be guided by controlled, randomized clinical trials. This should of course be considered especially in children. However, only a minority of drugs have been studied in formal trials on children.

Biologic response modifiers (Biologics) currently approved for treatment of JIA

Conventional therapy with methotrexate, leflunomide or sulfasalazine is often not successful in ameliorating disease especially in patients with polyarticular and systemic subtypes [3]. Extrapolating data of the only randomized trial with two active comparators, about 50% of the clinical disease activity persists despite prolonged treatment [10]. This warrants more efficient treatment for those patients who did not reach remission. A decade ago, as new biological treatment option, anti-Tumour-Necrosis-Factor-α (TNF-α) therapy has shown success in polyarticular JIA patients. TNF-α is a soluble 17kD protein produced by T-lymphocytes, monocytes and macrophages consisting of three identical subunits. It binds two specific receptors on the membranes of target cells, a 55kD and a 75kD receptor. After receptor binding the target cell is activated and triggers expression of proteins capable of further cell activation, cell adhesion and synthesis of prostaglandines, prostacyclines and other proinflammatory cytokines. Neutralization of TNF-α has beneficial effects in rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease and a number of further inflammatory conditions. Three different monoclonal antibodies, the chimeric antibody infliximab, the human antibodies adalimumab and golimumab a soluble TNF receptor fusion protein etanercept and the pegylated ant-TNF antibody F(ab)2 fragment certolizumab have been studied and approved for at least rheumatoid arthritis. They all bind to TNF-α and antagonize its effects while there seem some differences since adalimumab and infliximab proved to be valuable in chronic inflammatory bowel disease while etanercept does not. Monoclonal antibodies bind their target not only when it is free in the serum like etanercept, but also when it is bound to the cell surface which may be one explanation. Furthermore they differ in their binding affinity to TNF-α and in their biological plasma half life time which is 4-5 days for etanercept, 8-10 days for infliximab and 12-14 days for adalimumab, respectively. Accordingly the application intervals are different: etanercept 3-7 days, infliximab 28-56 days and adalimumab 7-14 days. Etanercept, adalimumab, golimumab and certolizumab can be self-injected subcutaneously at home. Due to possible infusion reactions infliximab has to be administered under clinical monitoring. Etanercept and adalimumab have been approved for treatment in children with JIA by the FDA and the EMA while infliximab is approved in children for treatment of Crohn’s disease only.
Numerous clinical and laboratory characteristics of systemic JIA can be attributed to direct influence of Interleukin-6 (II-6): acute phase reaction, leucocytosis, thrombocytosis, hypergammaglobulinemia, hepatosplenomegaly, osteoporosis, growth delay. IL-6 is a pleiotropic cytokine with proinflammatory effects on numerous cells, among them B-lymphocytes, T-lymphocytes, hematopoietic stem cells and also hepatocytes and osteoclasts. It is also synthesized by numerous different cell types: lymphocytes, monocytes, fibroblasts, synovioocytes and endothelial cells. In B-lymphocytes IL-6 induces the activation and maturation to antibody-producing plasma cells. C-reactive protein (CRP) as well as serum amyloid A are produced under the influence of IL-6. Plasma concentration of IL-6 correlates with disease activity and decreases under effective treatment.

Currently, two TNF-Inhibitors, adalimumab and etanercept, the cellular interaction inhibiting protein abatacept and the interleukin-6 receptor antibody tocilizumab are licensed for the use in children with juvenile idiopathic arthritis. It can be expected that there are patients who are sequentially treated with one or more of these biologic agents:

**Etanercept**

Etanercept has now been used in the treatment of active polyarticular juvenile arthritis in patients aged at least 4 years for 10 years after it has been proven to be greatly beneficial in a single randomised controlled study (6). It is a TNF-receptor-immunoglobulin-fusion protein, which binds both TNF-α and TNF-β (lymphotoxin-α) with high affinity. In a single placebo controlled trial with 69 children with polyarticular disease, who were refractory to previous treatment, Etanercept proved to be effective. Efficacy seemed to last over a period of up to 8 years [13,14].

The rate of adverse effects and serious infections was low, even with prolonged treatment. These observations in a few patients correspond with data from the German Etanercept long-term register, in which data of more than 1450 patients are recorded [15,16]. In this collective, 92% of patients were treated with etanercept for at least 1 year, 78% for at least 2 years and 66% for at least 4 years. The high adherence rate to this therapy suggests a favourable balance of efficacy and tolerability. Reported adverse events, e.g. local skin reactions, were generally mild and transient. Of special interest are the occurrence of infectious diseases, other autoimmune diseases (e.g. demyelinating diseases, uveitis) or demasking of other autoimmune diseases (e.g. Crohn’s disease), as well as new manifestations of malignoma and especially lymphoma. However, so far there is no apparent association between the occurrence of malignoma and treatment with etanercept while already biologics naïve JIA patients had a higher incidence of malignancies and especially lymphoma compared to controls [17-19].

**Adalimumab**

Adalimumab is a human monoclonal anti-TNF antibody. In Europe, adalimumab is available for treatment of patients with polyarticular JIA from the age of 13 either as monotherapy or in combination with methotrexate while in the USA adalimumab is already approved for treatment of children above the age of 4 years. In an open phase of a controlled clinical withdrawal trial of adalimumab for the treatment of JIA 171 patients were initially treated with adalimumab (24mg/sqm every other week s.c.) [20]. 84 of these patients continued a previous treatment with methotrexate. 88%, 80%, and 59% of patients on monotherapy and 95%, 92% and 82% of patients on a combination with Methotrexate showed a response according to PedACR 30, 50, and 70 criteria, respectively [21]. In the subsequent placebo-controlled phase of the trial disease flares were significantly less frequent in the adalimumab group. Thus, adalimumab demonstrated efficacy in treating polyarticular JIA. In the open long-term extension phase a dosage of 24 mg/sqm every other week was used. However, a change to a fixed dose of 20 mg every other week in children with a body weight below 30 kg and 40 mg every other week in children with a body weight of 30 kg or more did not result in a change of efficacy or tolerability. No tuberculosis, other opportunistic infections or malignancies were observed in this patient cohort while data on larger patient numbers are lacking so far.

Adalimumab seems valuable not only for treatment of arthritis but also for chronic recurrent anterior uveitis, which emerged in about 20% of JIA patients especially in oligoarticular JIA, seronegative polyarthritis and juvenile psoriasis arthritis [22].

In an open trial 16 of 18 patients with uveitis who had all failed systemic steroids, cyclosporine, MTX, leflunomide, etanercept or infliximab had good responses to adalimumab [23]. In another retrospective study on 20 patients with chronic uveitis of whom 19 previously were treated with infliximab or etanercept 7 patients showed improved activity, 1 patient worsening while in 12 patient there was no change in the activity of uveitis [24]. These studies suggest that adalimumab is a potential treatment option in JIA-associated uveitis. So far only open uncontrolled trials have indicated clinical usefulness while controlled trials are still ongoing.
Tocilizumab

Tocilizumab is a humanized antibody against the interleukin-6 receptor, which blocks the formation of a complex of interleukin-6 and interleukin-6 receptor. Bioactivity of IL-6 can be inhibited by the antibody tocilizumab.

Tocilizumab in systemic onset JIA

In a pilot study, patients with active refractory systemic JIA received a single infusion of 2, 4 or 8 mg/kg. Already 48 hours later improvements in all 18 children were detected, which lasted up to 4-8 weeks. 11 patients (61%) achieved an ACR JRA30 response [25].

In a dose escalating study with repeated application of tocilizumab 11 patients with active refractory systemic JIA initially received up to 3 infusions at a dose of 2 mg/kg every 14 days. In the absence of treatment success, the dose was increased to 4 mg and finally to 8 mg/kg each for up to 3 more infusions. Finally, 3 patients required infusions with a maximum of 2 mg/kg, 5 patients received a maximum of 4 mg/kg and 3 patients 8 mg/kg. 10 of the 11 children showed immediate improvement with a response to the PedACR30 criteria. 7% to the PedACR50 criteria. All patients showed an improvement in episodes of fever and arthritis. The medical laboratory parameters CRP, ESR acceleration, haemoglobin and platelet counts returned to normal during therapy.

In addition to uncomplicated infections, in these open label studies no clinical side effects were observed, but a rise in cholesterol and alanine aminotransferase as well as a decrease of gamma globulins [26]. Discontinuations were not necessary, serious adverse events did not occur.

One double-blind placebo-controlled study in 56 Japanese SJIA patients aged 2 to 19 years has been performed. During the open label 12 weeks initial phase of this placebo-controlled double-blind trial patients were treated with tocilizumab 8 mg/kg every other week over 6 weeks. 91% of patients showed a PedACR30 response. An immediate control of fever, leukocytosis, thrombocytosis, CRP- and ESR-elevation could be demonstrated. Patients having at least a PedARP30 and low CRP of less than 5 mg/l had been randomized to double-blind receive either placebo or to continue tocilizumab treatment for 12 weeks. In this placebo-controlled phase in the placebo group disease flares were significantly more frequent. 83% of patients in the placebo group but in only 20% of patients in the tocilizumab group reach the primary end point of a flare of the disease. Only 4 (17%) patients in the placebo group and 16 (80%) of the tocilizumab group had at the end of the double-blind phase, at least reached the PedACR30 criteria + low CRP (p <0.0001) [27].

In the open label wash phase of the study there were two serious adverse events, an anaphylactic reaction in a patient without anti-tocilizumab antibodies of the IgE-type and gastrointestinal bleeding in the other patient. In the double blind phase of the study, one infectious mononucleosis with a significant increase in transaminases and leukopenia occurs and one patient in the placebo group had a herpes zoster. The number of non-serious adverse events on tocilizumab was similar to that of the placebo group. However, safety assessment is limited as to all patients previously had entered the open label wash phase in phase of the trial and had been exposed to the drug. No opportunistic infection or death occurred. A macrophage activation syndrome was not observed. The patients were thereafter offered to participate in an open label extension study for an additional 48 weeks. At the end of this study 47 (98%), 45 (94%) and 43 (90%) of patients were responders according to the PedACR 30/50/70 criteria.

Long-term studies with Tocilizumab in systemic onset JIA

Overall, 128 patients from several phase II and phase III studies participated in an open label extension study to examine the long-term tolerance and safety. Here, all patients received tocilizumab 8 mg/kg intravenously every 2 weeks. At the beginning, the patients were on average 9 years old and have had a disease duration of 4 years. The mean duration of therapy was 78 weeks. In only 14 patients, the therapy was terminated prematurely. In 8 cases on grounds of incompatibility, in 5 patients due to IgE antibodies to tocilizumab and only 1 patient because of ineffectiveness. Adverse events occurred in 120 patients (94%), resulting in a rate of 787 per 100 patient-years. Serious adverse events and serious infections occurred at a rate of 37 and 14.5 per 100 patient-years. The most common events were diarrhoea (3.8/100 patient-years) and pneumonia (3.4/100 patient-years). Macrophage activation syndrome (MAS), anaphylaxis (n = 2), cardiac amyloidosis, a duodenal wall or gastrointestinal bleeding all lead to discontinuation of therapy. Two patients died, one of MAS and one of cardiac amyloidosis. Opportunistic infections, tuberculosis, or the new onset of autoimmune disease were not observed. Sustained remission of the disease even after treatment with tocilizumab was reported in 4 patients [28].

In the global double-blind placebo-controlled TENDER trial 120 patients with active systemic onset JIA (age range, 2–17 years) with a previous inadequate response to NSAIDs and corticosteroids were randomly assigned in a 2:1 ratio to receive tocilizumab every 2 weeks (8 mg/kg for patients >30 kg body weight; 12 mg/kg for patients <30 kg) or placebo [29].
Significantly more tocilizumab patients reached the primary endpoint of a PedACR30 response plus absence of fever (85% vs. 24%; \(p<0.0001\)). Additionally, significantly more patients on tocilizumab achieved a PedACR50/70/90 response at week 12 compared to controls. Of the patients who had fever, anaemia or thrombocytosis at baseline, significantly more tocilizumab patients than controls had no fever, had normal haemoglobin levels and normal platelet counts at week 12. The responderate was not influenced by the number of affected joints, nor by the presence of fever at initiation of treatment. Pre-treatment with anakinra has no negative impact on the effectiveness of tocilizumab while patients with no prior TNF inhibitor therapy had a slightly better response than those who have been exposed to TNF-antagonists. The combination with MTX had no effect on the efficacy of tocilizumab in this trial. Serious adverse events were rare: angioedema, urticaria, varicella infection and bacterial arthritis resolved without sequelae. According to these results tocilizumab seems to be highly effective in treating systemic onset JIA.

**Tocilizumab in Polyarticular JIA**

Polyarticular juvenile idiopathic arthritis (pJIA) consists of 3 subsets of JIA as defined by the International League of Associations of Rheumatology (ILAR) (Petty, 2004):

- Rheumatoid factor (RF) positive pJIA
- RF-negative pJIA
- Extended oligoarticular JIA (extOA)

Given the efficacy and safety of TCZ in pJIA in Chugai studies MRA318JP and MRA319JP, coupled with the success of TCZ in treating adult rheumatoid patients there was clinical support for pursuing this indication for pJIA further.

The pivotal study CHERISH was a three-part, two-year, phase 3 randomised withdrawal study investigating the efficacy and safety of tocilizumab (TCZ) in patients with pJIA. Part I was a 16 week active-treatment lead-in for all patients followed by Part II a 24 week placebo controlled double-blind withdrawal, period this was then followed by a long term open label follow up period with all patients receiving tocilizumab. The study met its primary endpoint at Week 40 with a significantly higher proportion of placebo patients experiencing a JIA ACR30 flare between Week 16 and Week 40 relative to Week 16 compared to the all TCZ patients (48.1% vs 25.6% \(p = 0.0024\)).

The majority (168/188, 89.4%) of patients attained the required JIA ACR30 response by Week 16 and thus entered the withdrawal phase. At Week 40, patients who continued on TCZ after Week 16 showed higher JIA ACR responses than those who were randomized to receive placebo. Through Week 40, use of TCZ was well tolerated and there were no additional safety concerns noted in this pJIA patient population compared to that observed in the adult RA population. The AEs observed were consistent with the known safety profile for TCZ.

**Abatacept**

Abatacept is a CTLA4-IgFc-fusion protein with long plasma half time for therapeutic use. The mechanism of action of abatacept is significantly different from that of other biologics. For stimulation of T cells an interaction of the T-cell receptor (TCR) with the HLA class 2 antigen of the antigen-presenting cell (APC) is crucial, as well as an interaction between accessory membrane antigens. By interaction between CD28 on T-cells and CD80 and CD86 on antigen-presenting cells, the T cell is stimulated. The CTLA4 antigen on T-cells may also enter into an interaction with CD80/CD86 resulting into anergy or even apoptosis. Abatacept binds to CD80/CD86 on antigen-presenting cells thereby preventing T-cell activation.

In a double-blind randomized placebo-controlled study, 190 patients with polyarticular JIA were initially treated with abatacept for 4 months at a dose of 10 mg/kg monthly [30]. After 4 months, 123 of 170 remaining patients showed a response to the PedACR30 criteria. 76% of patients not previously treated with TNF-inhibitors achieved a response according to the PedACR30, 60% a PedACR50 and 36% a PedACR70 response. 13% achieved clinical remission (inactive disease). Patients who have previously been exposed to TNF-inhibitors had a significantly less frequent response to therapy (PedACR30/50/70 in 39%/25%/11%). The response rate to therapy in all JIA subgroups was comparable. In the following placebo-controlled double-blind phase, significantly more patients in the placebo group had disease flares compared with patients receiving abatacept. 33% of placebo patients but only 20% of abatacept patients in the 6 month study period showed a relapse \(p = 0.0003\). The PedACR50 response rate increased until the end of the 6 month controlled phase to nearly 80% of patients receiving abatacept, with over 50% of patients showing a PedACR70 response [30]. Abatacept is applied intravenously in a dosage of 10 mg/kg at weeks 0, 2, 4 and then every 4 weeks. In contrast to TNF-antagonists
clinical effects of abatacept set in with a delay and usually increase with continuation of therapy over several months.

The tolerability of abatacept in the phase III clinical trial was good. There were no more adverse events than in the placebo group. One case of acute lymphatic leukaemia was observed in a patient who at inclusion already had a conspicuous blood count. In the double blind phase, no serious adverse events were observed. 12 patients experienced new antinuclear antibodies, antibodies to double-stranded DNA occurred in 9 patients. Clinically, there were no cases of lupus.

Abatacept has been approved for treatment of JIA patients of 6 years or older with polyarticular arthritis in patients refractory or intolerant to TNF-inhibitors although this subgroup of patients to a much lesser extend responded to treatment than biologic naïve patients.

Canakinumab

Interleukin-1β (IL-1β), a proinflammatory cytokine produced by monocytes/macrophages and dendritic cells, induces the expression of numerous proinflammatory genes, among them the one coding for cyclooxygenase 2 (COX 2), which is important in rheumatic inflammation processes including fever. IL-1 seems to be a major mediator of the inflammatory cascade especially important in systemic onset JIA. Systemic onset JIA patients’ mononuclear cells spontaneously produce large amounts of IL-1 and patients’ sera could provoke IL-1 synthesis in cultures of mononuclear cells from healthy controls making this cytokine an interesting target for therapy of this disease.

Canakinumab, a human IL-1b antibody with prolonged plasma half-life binds selectively to IL-1b without interfering with IL-1RA. It is administered as a subcutaneous injection once monthly. Its efficacy in the treatment of genetic fever syndromes makes canakinumab an interesting option for use in systemic arthritis [31]. In a Phase II trial performed in children with systemic JIA, an open-label dose-escalation study, 23 children and adolescents (age 4-19 years) received a single injection of canakinumab s.c. escalating from a dosage of 0.5 to 9 mg/kg [32]. A new dose was administered at the time the disease flared. Thirteen of 22 (59%) patients showed an immediate response, reaching at least a PedACR50 already on day 15. An inactive disease was achieved in four patients (18%). Seventeen of 23 patients were previously treated with Anakinra. Six of 11 nonresponders to Anakinra achieved at least a PedACR50 on day 15 after a single dose of canakinumab. The best baseline predictor of improvement was a lower number of active joints, an observation which seems similar to the experience with anakinra. The median time to re-recognizable disease activity was 56 (95% CI: 32 - 100), 60 (38 - 95), and 90 (45 - 181) days for doses < 3 mg/kg, 3 mg/kg, and > 3 mg/kg, with a probability of relapse within 1 month from 19% (95% CI: 6 - 41), 17% (6 - 34), and 7% (1 - 23). The injections were well tolerated. Adverse events were mild to moderate in severity and consisted mainly as infections and gastrointestinal disorders. Three serious adverse events occurred. In a placebo-controlled double-blind study in systemic JIA patients with a single s.c. injections of canakinumab 84 patients received canakinumab or placebo [33]. On day 15, 84% versus 10% achieved the primary end point of a modified PedACR30. As early as day 3, significant improvement of systemic symptoms and arthritis was evident in the canakinumab group. In both groups, one patient each developed MAS and further one patient in each group a serious infection. In a further randomized trial with a withdrawal design 177 patients received canakinumab 4 mg/kg, maximal 300 mg every 4 weeks. In the open label part 1 of the trial all patients received canakinumab and tapering of preexisting corticosteroids was attempted before patients entered the double-blind placebo-controlled part of the trial. Fortytwo of 92 patients (46%) on corticosteroids could reduce the dosage by at least 50% and 42 of 128 patients (33%) discontinued corticosteroids. One hundred patients were admitted to the randomized part of the study. Here, the median time to flare was 236 days (95%CI: 141-449 days) for placebo and was not determinable for canakinumab because less than 50% had flared, corresponding to a 63% relative risk reduction in flare. Thereafter all patients were transferred to an ongoing open-label observational study. MAS occurred in further two patients, of whom one died. In summary, canakinumab turned out to be highly effective in systemic JIA [33].

6. Registry objectives

6.1. Primary objectives

In this long term project so-JIA children undergoing treatment with tocilizumab are documented for following objective:

• Safety and efficacy (clinical response according to the PedACR30/50/70 criteria) of treatment with tocilizumab in systemic onset juvenile idiopathic arthritis (so-JIA).
• Safety and efficacy (clinical response according to the JADAS-10 criteria) of treatment with tocilizumab in polyarticular juvenile idiopathic arthritis (pJIA).

The safety objectives for the study are as follows:

• To assess in routine clinical practice the rate of serious adverse events and the rates of serious events in predefined categories of special interest (infections, cardiovascular events, malignancies, and gastrointestinal perforations) in pJIA patients treated with TCZ or a comparator biologic

• To assess in routine clinical practice the rate and treatment outcome of uveitis in pJIA patients treated with TCZ or a comparator biologic

• To assess in routine clinical practice the growth (relative to age-specific standards for height and weight) of pJIA patients treated with TCZ or a comparator biologic

• To assess in routine clinical practice the development (relative to onset of menarche [for females] and pubertal changes) of pJIA patients treated with TCZ or a comparator biologic

The effectiveness objectives for the study are as follows:

• To assess in routine clinical practice the effectiveness of TCZ in patients with RF positive and RF-negative pJIA, as determined on the basis of Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10)

• To assess in routine clinical practice the effectiveness of 10 mg/kg TCZ in pJIA patients weighing ≤ 30 kg at treatment initiation, as determined on the basis of JADAS-10. In addition, efficacy according to the PedACR30/50/70 criteria will be assessed

6.2. Secondary objectives

Secondary

• To assess the long-term efficacy on remission (criteria described by Wallace et al. including the presence of fever) of tocilizumab and the long-term efficacy on joint erosion, joint damage and treatment adherence in subjects with so-JIA and pJIA.

• To evaluate effectiveness of 10 mg/kg TCZ in pJIA patients weighing < 30 kg.

• To evaluate effectiveness of 8 mg/kg TCZ in pJIA patients weighing ≥ 30 kg.

• To evaluate effectiveness of TCZ in patients with RF-positive and RF-negative pJIA.

• To identify potential predictors of clinical response and remission.

• To assess treatment duration, dosing and reasons for dose modifications.

• To assess changes in co-medications, for example reduction of corticosteroids.

• To assess patient growth, development and bone density (if available).

• To assess the occurrence of fractures (fracture rate and location of fractures).

• To assess numbers and incidence rates of adverse events (AEs), AEs of special interest and serious AEs (SAEs).

• To assess treatment interruptions and treatment withdrawal due to AEs.

• To compare incidence rates of adverse events (AEs) and serious AEs (SAEs) observed in JIA patients with incidence rates in JIA subjects treated with TNF-inhibiting biologics and JIA patients treated with methotrexate (MTX). These patients treated with TNF-inhibiting biologics and MTX treated patients are already followed in a control registry. This will include but will not be limited to the evaluation of the
effect on: bone marrow, liver, lung, kidney, neurological, skin and gastrointestinal, serious opportunistic infections, and malignancies.

- To establish different cohorts of children (treated with anti-TNF- biologics ± MTX, tocilizumab ± MTX, MTX alone, not treated with MTX or biologics) each of which will be used as controls for the others.

7. Investigational plan

7.1. Overall registry design and plan description

The treatment decision on any biologic has been made by the treating physician before his decision to document the patient in this registry.

All patients with so-JIA and pJIA who have agreed to participate in this register should be observed over a period of at least 5 years and 10 years, respectively. In continuation of therapy, the observation period is extended.

Patients, who have completed treatment with tocilizumab will be recorded in the registry for at least 3 years.

The registry will analyze the frequency and severity of AEs, AEs of special interest and SAEs during treatment with biologic agents approved for treatment of the respective category of juvenile idiopathic arthritis.

AEs of special interest will be reported with the same reporting timelines and on the same reporting form as SAEs.

In addition any pregnancy will be reporting and analyzed.

7.2. Selection of registry population

Subjects will be male and female children of any race or ethnicity with systemic onset juvenile idiopathic arthritis (soJIA) and polyarticular juvenile idiopathic arthritis (pJIA), age from 2 to <18 with an active disease who start treatment with tocilizumab (incident patient cohort).

Patients newly treated with tocilizumab or with tocilizumab and MTX will be enrolled.

In addition a prevalent patient population already on treatment with tocilizumab will be followed as well (prevalent patient cohort).

As control group a MTX treated patients group will be used in sJIA. This cohort is also followed. These patients have not been treated at any time with a biologic.

A control group of pooled patients treated with biologics (mainly TNF-inhibitors) other than TCZ will be followed for pJIA. Comparisons to single biologic therapies will not be made.

Comparator patients will be enrolled concurrently with the TCZ patients.

Number of subjects

so-JIA: Unrestricted (we expect to recruit about 50 patients/year).

pJIA: The total number of newly recruited pJIA patients will be approximately 250 patients per year. Of which, approximately 75 patients per year will initiate tocilizumab.

Number and type of centers
Unlimited (we expect to recruit 70 centers in Germany).

7.3. Inclusion criteria

To be eligible for enrollment in the registry, subjects must meet the following criteria:

I 1 Diagnosis of systemic onset or polyarticular JIA as determined by Edmonton International League of Associations for Rheumatology (ILAR) criteria.

I 2 Newly started therapy with tocilizumab for the incident patient cohort, patients already treated with tocilizumab for the prevalent patient cohort.

I 3 Parents / legal guardian and patient are willing to participate in the registry and signed voluntarily the Informed Consent form.
I 4 Patient is at least 2 years old and has not reached his 18th birthday.

I 6 The patient is suitable according to the physician for treatment with tocilizumab.

7.4. Exclusion criteria

E 1 Any contraindication listed in the German ‘Fachinformation’ of the drug tocilizumab.

E 2 Other diagnoses as systemic onset or polyarticular JIA, which leads to treatment with tocilizumab.

E 3 Pregnant patients.

8. Registry Conduct

8.1. Visit sequence

Physicians will be provided with a registry kit, that includes the registry protocol, a CRF including AE reporting form, parental informed consent and patient assent forms, SAE and pregnancy forms.

The doctor guides the patient through the regular scheduled visits by routine clinical practice.

The investigator will complete the first questionnaire at the enrolment visit (baseline).

The investigator will monitor the patients during regular visits. It may be possible that neither the patient nor the investigator, between visits from the registry, will be contacted. This data is not recorded by the registry. The relevant information closest to the registry visit entry date of the observation period will be required.

The physician should decide with the patient to stop treatment with tocilizumab. The physician must first complete an early termination form and then a further follow up examination of the patient every 6 months for at least 3 years.

The procedures are performed in registry are listed in figure 1.
**Figure 1: Registry activities**
(in German language since the registry will recruit patients in Germany only)

<table>
<thead>
<tr>
<th>Unterlagen als Erstausstattung in der Patientenmappe</th>
<th>Bei Therapiewechsel oder Therapieende</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base-line</strong></td>
<td><strong>Monat 3</strong></td>
</tr>
<tr>
<td>Honorarvereinbarung</td>
<td>x</td>
</tr>
<tr>
<td>Einschreibung</td>
<td>x</td>
</tr>
<tr>
<td>Einverständniserklärung</td>
<td>x²</td>
</tr>
<tr>
<td>Patienteninformation</td>
<td>x²</td>
</tr>
<tr>
<td>Elterninformation</td>
<td>x²</td>
</tr>
<tr>
<td>Ersterhebungsbogen (2 Seiten)</td>
<td>x</td>
</tr>
<tr>
<td>Fragebogen zur Gesundheitsbewertung im Kindesalter (2 Seiten)</td>
<td>x</td>
</tr>
<tr>
<td>Therapieverlauf</td>
<td>x</td>
</tr>
<tr>
<td>Unerwünschtes Ereignis (UE)</td>
<td>(x)¹</td>
</tr>
<tr>
<td>Schwangerschaft</td>
<td>(x)¹</td>
</tr>
<tr>
<td>Abbruch</td>
<td>(x)¹</td>
</tr>
</tbody>
</table>

(x)¹: Bei Bedarf auszufüllende Dokumente im Falle von Nebenwirkungen und/oder Therapieabbruch
x²: Diese Dokumente verbleiben aus datenschutzrechtlichen Gründen beim behandelnden Arzt
8.2. Baseline characteristics

Informed consent

Signed informed consent will be obtained from the parents or legal guardian before any registry documentation are undertaken. The patient will be included in all discussions in order to obtain oral or written consent regarding data protection.

Demographic data

- Date of birth
- Gender
- Family income
- Race
- Ethnicity

History of juvenile idiopathic arthritis (JIA)

- Month / year of onset of specific complaints and diagnosis, resp.
- Presence of ANA, HLA-B27 or anti-CCP-antibodies
- Presence of RF-antibodies
- Previous medication at any time and dosage
- Comorbidities and special infection history, and history of uveitis

8.3. Treatment with tocilizumab and dosing change

Before the patient is included in the register, the doctor has prescribed the patient tocilizumab. At each visit, the doctor recorded the start and possibly the end of the administration of medication, possible changes in the dosage and exposure and their causes since the last visit.

8.4. Product Supply

None. The registry documents the routine treatment of sJIA or pJIA children.

The patients received the conventional commercial product by prescription. The registry is not responsible for the medication.

8.5. Assessment of disease activity and physical function

Joint assessment

At each visit the joints of the patient will be examined for pain, swelling and limited movement in order to assess the activity of the arthritis.

Laboratory efficacy variables

The following variables are regarded as laboratory efficacy variables:

- CRP [mg/L]
- ESR [mm/h].

Assessment queries

- The doctor and the patient assessment of disease activity and treatment responses
- Parent/patient & Physician's Global Assessment of Disease Activity (VAS)
- Assessment of the physician regarding treatment response.
• Assessment of the parent/patient regarding treatment response.
• CHAQ (Childhood Health Assessment Questionnaire), German version

**Inactive disease assessment**

The existence of factors attributable to JIA indicating active disease are as follows:

• Active arthritis
• Fever
• Rash
• Serositis
• Splenomegaly
• Generalized lymphadenopathy attributable to JIA
• Active uveitis

In addition, the morning stiffness and duration is recorded.

Bone density data are documented as far as routinely available.

The influence of tocilizumab treatment on the occurrence/ treatment of uveitis in pJIA patients treated with TCZ and biologics other than TCZ will be assessed.

**8.6. Safety variables**

Documentation of adverse events

Adverse events (serious and non-serious) will be documented in the whole course of observation:

• beginning with signing of the Informed Consent
• ending at least 5 years and 10 years after inclusion for so-JIA and pJIA, respectively.

Details are given in section 9. Adverse events.

In the case of early termination of therapy on a separate form the reason for this and the subsequent treatment decision are recorded:

• Lack of effectiveness
• Request of the patient
• Side effects/intolerance
• Remission of the disease
• Other reasons

Patients who discontinued treatment with tocilizumab will be followed by the registry for at least 3 years after discontinuation.

Pregnancy will be documented in the whole course of the observation and up to 3 months after last treatment with tocilizumab.

**8.7. Vital signs, body weight, height**

Blood pressure and pulse rate will be measured with the subject in sitting position. These variables, body weight, and height as well as development according to Tanner stage and occurrence of menarche, will be measured at screening, baseline, each study visit, early withdrawal, and at follow-up visit.

**8.8. Appropriateness of measurements**

Standard statistical, clinical and laboratory procedures will be used in this registry.

All efficacy measurements in this registry are standard and validated. All clinical and laboratory procedures in this registry are standard and generally accepted.
9. Adverse events / pregnancy

The investigator will monitor each subject for clinical and laboratory evidence of adverse events / pregnancy on a routine basis throughout the follow up. The investigator will assess and record any adverse event / pregnancy in detail on the adverse event form / pregnancy form including the date and time of onset, description, severity, time course, duration and outcome, relationship of the adverse event to tocilizumab an alternative etiology for events not considered 'probably related' to tocilizumab, final diagnosis, if known, and any action(s) taken. For adverse events to be considered sporadic, the events must be of similar nature and severity. Adverse events / pregnancy whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be reported on the appropriate form. All adverse events / pregnancy will be followed to a satisfactory conclusion.

9.1. Definitions

Adverse event

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from therapy, necessitate therapeutic medical intervention, meet protocol-specific criteria.

A treatment-emergent adverse event is defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of study drug is administered until 90 days have elapsed following discontinuation of study drug administration.

All adverse events will be documented and graded for severity, seriousness and causality. International definition for seriousness will be used (see below).

Adverse events of special interest

Adverse events of special interest are:

- Anaphylaxis/ Hypersensitivity
- Autoimmune diseases
- Bleeding events
- Chronic inflammatory bowel disease
- Cytopenia
- Demyelinating disorders
- Gastrointestinal perforations and related events
- Hepatic events
- Infections (including opportunistic infections)
- Macrophage activation syndrome (MAS)
- Malignancies
- Myocardial infarction/ acute coronary syndrome
- Pregnancy/-outcome, Follow Up (Child)
- Stroke
- Systemic lupus erythematosus
A specific adverse event processing will be implemented including MedDRA-Coding. The German language free term of the adverse event will be translated into an English language free term. These free terms will be processed to Low level Term (LLT), further to the Preferred Term (PT), further to the High Level Term (HLT) and finally to Standard Organ Class (SOC) term.

CIOMS Listings of all AEs will be provided every 6 months to Roche Pharma AG (to the Drug Safety Department (contact details see 9.5) and the responsible Medical Manager).
Pregnancy

Pregnancies must be reported to Prof. Dr. Gerd Hornemann or the BIKER Registry secretary (Details see 9.5) by the investigator within one working day using the Pharmachild JIA registry pregnancy report form.

9.2. Relationship to the respective biologic agent

The investigator will use the following definitions to assess the relationship of the adverse event to the use of the respective biologic agent:

- **Probably related**: An adverse event has a strong temporal relationship to the respective biologic agent or recurs on re-challenge and another etiology is unlikely or significantly less likely.
- **Possibly related**: An adverse event has a strong temporal relationship to the respective biologic agent and an alternative etiology is equally or less likely compared to the potential relationship to the respective biologic agent.
- **Probably not related**: An adverse event has little or no temporal relationship to the respective biologic agent and/or a more likely alternative etiology exists.
- **Not related**: An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the respective biologic agent (e.g. has no temporal relationship to the respective biologic agent or has a much more likely alternative etiology).

If an investigator's opinion of possibly, probably not, or not related to the respective biologic agent is given, an alternative etiology must be provided for the adverse event.

9.3. Outcome

The outcome of an adverse event is assessed by the investigator using the following definitions:

- **Recovered completely**: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the Informed Consent.
- **Not recovered/ Persisting**: The subject's condition has not improved and the symptoms are unchanged.
- **Recovered with sequelae**: As a result of the AE the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be classified as SAE.
- **Unknown**
- **Fatal**: Exitus, any
- **Improved**: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the adverse event collection period.
- **Worsened**: The condition has worsened since the initial report

9.4. Adverse event collection period

Serious adverse events are to be collected from the time the subject signs the registry-specific Informed Consent form. Serious adverse events will be collected for the total observation period regardless of the continuous application of tocilizumab or if treatment has been discontinued or changed. Adverse events of interest will be requested in the same manner.

All serious and non-serious adverse events occurring from the time of tocilizumab administration until 90 days following the last dose of study drug administration have elapsed will be collected, whether elicited during scheduled visits and/or telephone contacts or spontaneously reported by the subject.
Adverse event information will be collected and recorded on the appropriate form as shown in figure 2, Adverse event collection:

**Figure 2: Adverse event collection**

<table>
<thead>
<tr>
<th>Consent signed</th>
<th>Administration of first dose of drug</th>
<th>Administration of last dose of drug</th>
<th>90 days after administration of last dose of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE adverse event</td>
<td>SAE serious adverse event</td>
<td>AESI adverse event of special interest</td>
<td></td>
</tr>
</tbody>
</table>

### 9.5. Reporting of adverse events

In the event of a serious adverse event or an adverse event of special interest, whether related to study drug or not, the investigator will notify the following people within 1 working day of being made aware of the SAE using the adverse events form 1/2.

The investigator will notify the following people within 1 working day of becoming aware of a pregnancy using the registry pregnancy report form:

Center of General Pediatrics and Neonatology
Asklepios Clinic Sankt Augustin
Arnold-Janssen-Straße 29
53757 Sankt Augustin

In the event of a serious adverse event or an adverse event of special interest whether related to study drug or not, or pregnancy, Prof. Horneff will notify the following within 1 working day of being made aware of the event using the Pharamchild JIA registry moderate, severe or serious adverse event report 1/2:

- Arzneimittelsicherheit Roche Pharma AG
  - Fax: +49 (0)7624-14-3183
  - Mail: grenzach.drug_safety@roche.com
- Pfizer Arzneimittelsicherheit Germany
  - Fax: +49 (0)30 550054 51069
- Arzneimittelsicherheit AbbVie Deutschland GmbH & Co. KG
  - Fax: +49 611-1720-1628
9.6. Pregnancy

The registry and Roche Drug Safety (Arzneimittelsicherheit) must be notified immediately if a female registry subject becomes pregnant during the treatment with tocilizumab (see Section 9.5 Reporting of adverse events, for contact information).

If a patient becomes pregnant during surveillance of the register and discontinued therapy with tocilizumab, she will continue to be monitored in the register. The course and the outcome of the pregnancy will be documented.

The medical outcome of an induced or a spontaneous abortion is considered a serious adverse event, and must be reported to the registry within one working day of learning of the event.

10. Data quality assurance

Before inclusion in the register, parents must have signed the consent form. Children > 12 years were to sign the patient information as well. Only then can begin the documentation of the patient. The signed parental and patient information remains in the patient record. The data collected by the investigators are reviewed by the registry and submitted electronically. Not collected or non-unique data to be sent by the investigators.

The Sponsor will be responsible for data management of this study, including quality checking of the paper CRF data. Data were provided either by paper CRF or eCRF. In the case paper CRF is chosen, data will be double-entered by registry staff. In the case the eCRF option is chosen, data entered manually by the site will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system’s audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor’s standard procedures.

11. Source data verification and Case Report Form completion

11.1. Source documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects’ diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or X-rays.

11.2. Case Report Forms

The registry will supply case report forms (CRFs). These forms will be used to transmit information collected during this registry to the registry. CRFs must be completed for each subject enrolled in this registry. All CRFs must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, and must be initialed and dated by the investigator or his/her designee. Data are not to be obliterated by blacking out, correction fluid, or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g. transcription error) should accompany the change. The original of the CRFs remains with the investigator, a copy is faxed to the sponsor.

12. Statistical methods and determination of sample size

All analysis will be performed in a descriptive manner for so-JIA and pJIA. The pJIA patients will include a control group of pooled patients treated with biologics other than TCZ.
12.1. Demographic and baseline characteristics

Demographic and baseline characteristics of the patients will be reported using n (sample size), mean, standard deviation, minimum, median, and maximum for continuous variables, and counts and percentages for discrete variables, respectively. The Statistical Analysis Plan will provide the complete details of methods that will be used in analyzing the collected data.

12.2. Subject population

Subjects between the ages of 2 and < 18 years with systemic onset or polyarticular juvenile arthritis who meet the inclusion criteria mentioned in Section 7.3., Inclusion Criteria, and do not meet any of the exclusion criteria mentioned in Section 7.4. Exclusion Criteria, are eligible for this registry.

12.3. Analysis of efficacy

Both, the primary and the secondary objectives of the registry, safety and efficacy, will be analyzed in the Intention-To-Treat-population, including all patients who have been registered (included in the registry) and were exposed to the drug.

12.4. Analysis of safety

All subjects who received at least one dose of tocilizumab will be included in the safety analysis. Adverse events will be summarized in each treatment group by presenting both frequency and percentage. Events which are serious, related to tocilizumab, or which lead to premature discontinuation the treatment with tocilizumab will be separately summarized.

12.5. Determination of sample size

Due to the experience with the already existing registry for treatment of pJIA patients with etanercept and adalimumab, a recruitment rate of about 500 patients can be expected.

Assuming this total patient number (n = 500) within 5 years, a total exposure time of 1500 patient years can be expected.

For so-JIA a recruitment rate of 250 patients can be expected. Assuming this total patient number (n = 250) within 5 years, a total exposure time of 750 patient years can be expected.

Calculations of adverse events will be compared to the control group of patients treated with either TNF-inhibiting biologics which is build up in 2001 and followed since then or with methotrexate without biologics, which is followed since 2005. Here, actually 2100 patients treated TNF-Inhibitors and 1500 patients treated with MTX have been recruited with a recruiting rate of about 200 new patients yearly. For these patients a higher drop-out rate has to be assumed. At least a comparable number of patients and patient years can be expected.

13. Ethics

13.1. Independent ethics committee

Good Clinical Practice (GCP) requires that the registry protocol, any protocol amendments, the Informed Consent and all other forms of subject information related to the registry (e.g. advertisements used to recruit subjects) and any other necessary documents be reviewed by an Independent Ethics Committee (IEC).

13.2. Patient information and informed consent regarding data protection

The investigator or his/ her representative will explain the nature of the registry to the parents or legal guardian and the patient, and answer all questions regarding this registry. Prior to any registry-related visit procedures being performed on the subject, the Informed Consent statement will be reviewed and signed and dated by the
subject and the person who administered the Informed Consent. A copy of the Informed Consent/Informed Assent form(s) will be given to the parents or legal guardian and the original(s) will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that Informed Consent was obtained prior to any registry-related documentation and that the subject received a signed copy. The information for patients and parents and the respective Informed Consent/Assent forms are specified in the appendices.

14. Financial affairs

By signing the financial agreement the investigator agrees to receive a honorary for each documentation which is in compliance with the registry protocol the timely schedule.

15. Use of information and publication

15.1. Use of information

Reports will be provided in a routinely manner, i.e. twice yearly. In these reports, both safety and efficacy data will be provided.

Beside these reports, data of the registry will be used for interim analyses and verbal or written scientific publications.

15.2. Publication

Core publication(s) will be authored by specified principal investigator(s) who contribute significantly to the implementation and conduct of the registry and non-site personnel who contribute substantially to the design, interpretation or analysis of the registry.

Development of the core publication will be coordinated by a publication committee whose members will include investigators who provided significant input into registry design, implementation, conduct and interpretation.

A named author approach will be utilized only if this is a requirement of the journal selected for publication, or if additional publications are agreed (authors to be agreed upon by publication committee). The named author approach will need sanction of the publication committee. The listing will identify members of the publication committee, and if required by the selected journal, a contact for correspondence.

16. References


17. Abbreviations

Ab antibody
ACR American College of Rheumatology
Acro. Clav. acromioclavicular
AE Adverse Event
ag antigen
AMG German Medical Act (Gesetz über den Verkehr mit Arzneimitteln)
BASDAI Bath Ankylosing Spondylitis Disease Activity Score
BASFI Bath Ankylosing Spondylitis Functional Index
BSA Body Surface Area
BUN Blood Urea Nitrogen
BCG Bacillus Calmette-Guerin
CDC Center for Disease Control
cf. confer
CHAQ Childhood Health Assessment Questionnaire
CNS Central Nervous System
CPK Creatine Phosphokinase
CPMP Committee for Propriety Medicinal Products
CRF Case Report Form
CRO Contract Research Organization
CRP C-Reactive Protein
CSI Clinical supplies invoice
CTA Clinical Trial Authorization
DCF Data Clarification Form
DIP distal interphalangeal
DMARD Disease Modifying Anti-Rheumatic Drug
DR Data Review
DRR Data Review Report
dsDNA double-stranded DNA
ERA Enthesitis related Arthritis
e.g. e.g., for example
eow every other week
ESR Erythrocyte Sedimentation Rate
ETA Etanercept
etc.   etcetera
EudraCT European clinical trials database
extOA extended Oligoarthritis
FDA Food and Drug Administration
GCP Good Clinical Practices
GFR Glomerular Filtration Rate
HBs Hepatitis B surface
HCV Hepatitis C virus
i.a. intraarticular; if applicable
ICH International Conference on Harmonization
i.e. id est, that is
IEC / EC Independent Ethics Committee / Ethics Committee
IL interleukin
i.m. intramuscular
IMP Investigational Medicinal Product
IN Inclusion criterion
ITT Intention to Treat
i.v. intravenous
JAS Juvenile Ankylosing Spondylitis
JRA / JIA Juvenile Rheumatoid Arthritis, Juvenile Idiopathic Arthritis
LDH Lactate Dehydrogenase
LOM Limitation of Motion
MCP metacarpophalangeal
MTP metatarsophalangeal
n number
N/A not applicable
NCR no carbon required
NRS Numerical Rating Scale
NSAID Non-Steroidal Anti-Inflammatory Drug
PA posterior-anterior
PIP proximal interphalangeal
pJIA polyarticular juvenile idiopathic arthritis
PP Per Protocol
PPD Purified Protein Derivative
RA Rheumatoid Arthritis
RBC red blood cells
resp. respectively
SAE Serious Adverse Event
SAS Statistical Analysis System
Sc subcutaneous
SGOT / ALT Serum-glutamatic oxalacetic transaminase
SGPT / AST Serum-glutamate-pyruvate transaminase
SJC Swollen Joint Count
so-JIA systemic onset juvenile idiopathic arthritis
Sterno. Clav. sternoclavicular
Temp. mand. temporomandibular
TB tuberculosis
TJC Tender Joint Count
TNF Tumor Necrosis Factor
vs. versus
WBC white blood cells