# NI PASS PROTOCOL

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| **TITLE:** | **OBSERVATIONAL SAFETY AND EFFECTIVENESS STUDY OF PATIENTS WITH POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH TOCILIZUMAB** |
| **PROTOCOL NUMBER:** | WA29358 |
| **VERSION NUMBER:** | 6 |
| **REGISTRIES:** | May include, but not limited to, the following:<br>• Childhood Arthritis and Rheumatology Research Alliance (CARRA)<br>• Juvenile arthritis Methotrexate/Biologics long-term Observation (JuMBO)<br>• Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry) (BiKeR) |
| **TEST PRODUCT:** | Tocilizumab (RO4877533) |
| **DATE FINAL:** | Version 1: 24 August 2015 |
| **DATES AMENDED:** | Version 2: 18 November 2015<br>Version 3: 20 July 2016<br>Version 4: 27 July 2017<br>Version 5: 17 August 2018<br>Version 6: See electronic date stamp below. |

## PROTOCOL AMENDMENT APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 23-Apr-2020 18:58:49 | [redacted] EU QPPV | [redacted] |
| 24-Apr-2020 16:46:04 | Company Signatory | [redacted] |

## PROTOCOL AMENDMENT, VERSION 6:
## RATIONALE

Due to significant enrollment challenges, protocol WA29358 has been amended to complete this post-marketing requirement with a smaller number of registry patients, as agreed with the FDA and EMA.

Changes to the protocol, along with a rationale for the change, are summarized below:

- The proposed number of patients has been reduced. The original protocol proposed evaluating 800 patients (400 patients newly initiating tocilizumab (TCZ), 400 patients newly initiating a comparator biologic). In the amended protocol, enrollment will be stopped in June 2020, after the study has been open to enrollment for 5 years, and patients will then be followed for up to 5 years. It is expected that approximately 600 patients will have been enrolled (300 patients newly initiating TCZ, 300 patients newly initiating a comparator biologic) by June 2020. These changes are outlined in Section 5.1 “Study Design” and in Section 5.11 “Study Size”.
- The initial projected timeline of last patient enrolled has been revised accordingly throughout.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| BiKeR | Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry) |
| CARRA | Childhood Arthritis and Rheumatology Research Alliance |
| CRF | Case Report Form |
| CSR | clinical study report |
| DMARD | disease-modifying antirheumatic drug |
| *DSUR* | *development safety update report.* |
| EC | Ethics Committee |
| EMA | European Medicines Agency |
| eoJIA | extended oligoarticular juvenile idiopathic arthritis |
| FDA | Food and Drug Administration |
| GPP | Good Pharmacoepidemiological Practice |
| ICF | Informed Consent Form |
| IL-6 | interleukin 6 |
| IRB | Institutional Review Board |
| IV | intravenous |
| JADAS-10 | Juvenile Arthritis Disease Activity Score in 10 joints |
| *JADAS-71* | *Juvenile Arthritis Disease Activity Score in 71 joints* |
| JIA | juvenile idiopathic arthritis |
| JuMBO | Juvenile arthritis Methotrexate/Biologics long-term Observation |
| PBRER | periodic benefit-risk evaluation report |
| pJIA | polyarticular juvenile idiopathic arthritis |
| Q3W | every 3 weeks |
| Q4W | every 4 weeks |
| RA | rheumatoid arthritis |
| RF | rheumatoid factor |
| SC | subcutaneous |
| sJIA | systemic juvenile idiopathic arthritis |
| TCZ | tocilizumab |

## 1. RESPONSIBLE PARTIES

This protocol has been developed by Roche for submission to the health authorities and to identify the data that will be collected in response to postmarketing requirements. It will not be implemented as a protocol at registry sites. Rather, individual registries have implemented their own registry-specific protocols, which include collection of the specific data indicated in this protocol. To satisfy the postmarketing requirements, data will be collected from patients who are enrolled in national disease or treatment registries (hereafter referred to as "feeder registries"), which may include, but are not limited to, the following:

- Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry
- Juvenile arthritis Methotrexate/Biologics long-term Observation (JuMBO) registry
- Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry) (BiKeR)

The feeder registry protocols will be implemented at registry sites.

## 2. AMENDMENTS AND UPDATES

Any revisions to the protocol will be prepared by Roche or a designee to provide updated information to health authorities. The revised protocol will not be implemented at registry sites. Rather, individual registries will implement their own registry-specific protocols, which will include collection of the specific data indicated in this protocol.

Amendments to the feeder registry protocols will be prepared and submitted by the feeder registries to the Institutional Review Boards (IRBs)/Ethics Committees (ECs). Amendments to the feeder registry protocols may be submitted by Roche or the feeder registries directly to regulatory authorities, in accordance with local regulatory requirements.

## 3. MILESTONES

Study milestones are as follows:

| Study Milestone | Estimated Date [a] |
|---|---|
| Start of data receipt from feeder registries | October 2015 |
| End of receipt of data collection from feeder registries | *June 2025* |
| Annual reports of data from each individual feeder registry*, which are summarized in the PBRER/DSUR* | Annually *for feeder registry data, and summarized in the PBRER/DSUR following nationally agreed reporting periods* |

PBRER = periodic benefit–risk evaluation report; *DSUR = development* safety update report.

[a] The dates for the milestones are estimated dates and may be revised by the individual feeder registries.

# 4. RATIONALE AND BACKGROUND

## 4.1 BACKGROUND ON POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Polyarticular juvenile idiopathic arthritis (pJIA), as defined by the International League of Associations of Rheumatology (ILAR; Petty et al. 2004) is composed of several subsets of juvenile idiopathic arthritis (JIA). For the purposes of this study, pJIA will include the following subsets of patients as per the licensed indications in the United States and the European Union:

- Patients with rheumatoid factor (RF)-positive pJIA
- Patients with RF-negative pJIA
- Patients with extended oligoarticular JIA (eoJIA)

## 4.2 BACKGROUND ON TOCILIZUMAB

Interleukin 6 (IL-6) is a pleiotropic pro-inflammatory multifunctional cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. It was originally identified as B-cell stimulatory factor 2 because of its role in inducing the final maturation of B cells into antibody-producing cells. IL-6 has been shown to be involved in such diverse processes as T-cell activation, initiation of acute-phase response, and stimulation of hematopoietic precursor cell growth and differentiation. IL-6 is also produced by synovial and endothelial cells, leading to local production in joints affected by inflammatory processes such as JIA.

Tocilizumab (TCZ) is a recombinant humanized anti-human monoclonal antibody of the IgG1 subclass directed against the IL-6 receptor that inhibits the function of IL-6. Intravenous (IV) TCZ is currently being studied or has been studied in a variety of diseases, including Castleman's disease, multiple myeloma, systemic lupus erythematosus, Crohn's disease, ankylosing spondylitis, adult rheumatoid arthritis (RA), systemic JIA (sJIA), and pJIA. Subcutaneous TCZ has been studied in adult RA and is currently being studied in both sJIA and pJIA, as well as in giant cell arteritis, systemic sclerosis, and Takayasu arteritis.

Data from Study WA19977 (CHERISH; pivotal trial) and two Japanese studies (MRA318JP and MRA319JP) enabled the approval of TCZ IV in patients with pJIA in the United States in April 2013 and in the European Union in June 2013. TCZ SC administration was approved for the treatment of pJIA in the European Union in April 2018 and in the United States in May 2018 based on the results from the Phase Ib trial WA28117 (JIGSAW 117).

Following the approvals, separate postmarketing registry requirements were requested by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

## 4.3 STUDY RATIONALE

This protocol has been developed by Roche to meet the following requirements by the FDA and EMA.

The FDA requested "a long-term safety study in X pediatric patients 2–17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of pediatric pJIA patients. Patients should be followed for X years."

The EMA requested "a submission of the draft protocol of the registry as proposed by the MAH, collecting long-term efficacy and safety data in pJIA treatment. The registry will address, but not limited to, efficacy of 10 mg/kg for patients $<$30 kg; impact of the RF status on the efficacy of TCZ therapy; impact of TCZ therapy on the increased risk of atherosclerosis in RA patients, impact of TCZ therapy on growth development, influence of TCZ therapy on the occurrence/treatment of uveitis."

The EMA request for the study to address the impact of TCZ therapy on the "increased risk of atherosclerosis in RA patients" will be satisfied by the evaluation of cardiovascular events in patients with pJIA. In a previous communication on 17 January 2013 to the EMA, the rationale for evaluating cardiovascular events as a surrogate for atherosclerosis was accepted.

This protocol describes the collection, analysis, and reporting of aggregate and some patient data from the feeder registries to satisfy these postmarketing requirements to examine the long-term safety and effectiveness profile of TCZ in patients with pJIA in an observational setting, outside of a controlled clinical trial.

## 4.4 OBJECTIVES

The overall objective for the study is to assess the long-term safety and effectiveness of TCZ (IV or SC) in relation to comparator biologic in the treatment of pJIA in a real-world setting for 5 years.

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 adverse events in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious]) in pJIA patients treated with TCZ (IV or SC) or a comparator biologic
- To assess in routine clinical practice the rate and treatment outcome of uveitis in pJIA patients treated with TCZ (IV or SC) or a comparator biologic on the basis of available data from the feeder registries

- To assess in routine clinical practice the growth (relative to age-specific standards for height and weight) of pJIA patients treated with TCZ (IV or SC) or a comparator biologic
- To assess in routine clinical practice the development (via self-reported or examined Tanner staging) of pJIA patients treated with TCZ (IV or SC) or a comparator biologic on the basis of available data from the feeder registries

The effectiveness objectives for the study are as follows:

- To assess in routine clinical practice the effectiveness of TCZ (IV or SC) 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

# 5. RESEARCH METHODS

## 5.1 STUDY DESIGN

This is an international, multicenter, prospective, observational-cohort study to examine long-term safety and effectiveness data from patients with pJIA treated with TCZ IV 8 mg/kg (10 mg/kg in patients weighing <30 kg) Q4W or TCZ SC 162 mg Q2W (Q3W in patients weighing <30 kg) or a comparator biologic. Roche will obtain aggregate and some patient data from active feeder registries in the United States and the European Union, conduct periodic analyses, and report the associated results to the appropriate health authorities. Roche has confirmed that the feeder registries will collect all data points required to support the study endpoints. This protocol will not be implemented at the feeder registry sites and will not be approved by local IRBs/ECs. Rather, individual registries will implement their own registry-specific protocols, which will include collection of the specific data indicated in this protocol.

The study will allow for analysis of aggregate and some patient-level data from approximately *600* patients with pJIA (defined as RF-positive pJIA, RF-negative pJIA, or eoJIA per ILAR classification (Petty et al. 2004) who are enrolled in national disease or treatment registries (i.e., feeder registries) in the United States and Germany, at approximately 100 sites. The feeder registries may include, but are not limited to, the CARRA, JuMBO, and BiKeR registries. Data may also be collected from patients in other countries, including Canada, Puerto Rico, and Israel, at sites affiliated with these registries. Approximately *300* patients will be initiating treatment with TCZ (IV or SC), with or without a non-biologic disease-modifying antirheumatic drug (DMARD), and approximately *300* patients will be initiating treatment with a comparator biologic, with or without a non-biologic DMARD. The decision to prescribe TCZ (IV or SC) or a comparator biologic should be made by a physician and patient without regard to potential participation in any of the feeder registries, and there is no protocol-mandated

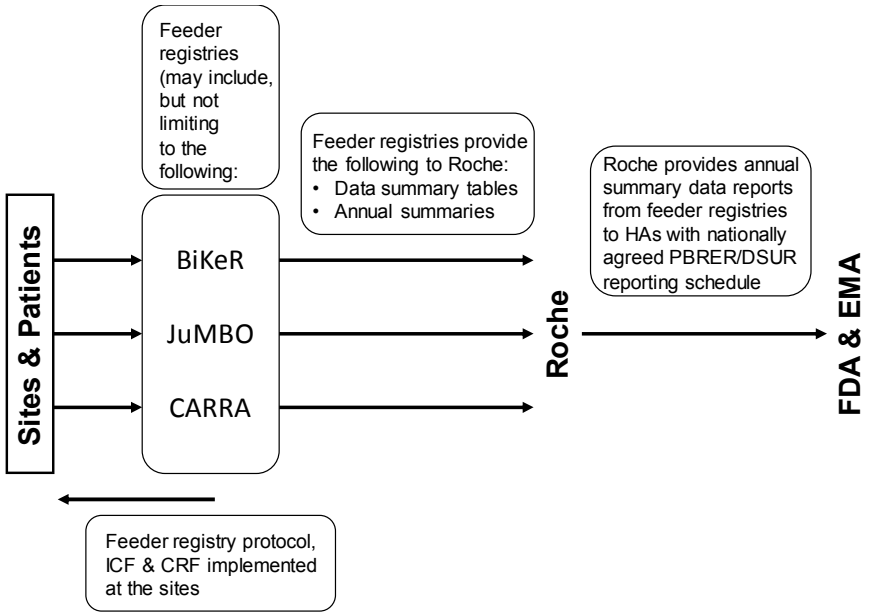
treatment assignment in the feeder registries. Patients will be evaluated and treated according to their physician's standard practice and discretion.

The observation period for this study is defined as a maximum of 5 years for patients initiating treatment with TCZ (IV or SC) or a comparator biologic. Data for the study will be collected directly from the feeder registries. Patients who switch therapy or discontinue therapy during the observation period will continue to be followed in accordance with the feeder registry protocols to allow for long-term safety assessment up to the maximum period of 5 years.

This study will start with the receipt of aggregate data from the feeder registries, estimated to be October 2015, and will end with the receipt of the last aggregate data, estimated to be *June 2025*. Some patient-level data will be received only upon study completion. During the study period, the feeder registries will produce annual reports *based on summary data reports. This information will be supplied to the Agencies in alignment with the nationally agreed* TCZ periodic benefit-risk evaluation report (PBRER)/*development* safety update report (*DSUR*) periods *and will be* based on summary data reports.

The study design is summarized in Figure 1.

**Figure 1 Study Design**




BiKeR = Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry); CARRA = Childhood Arthritis and Rheumatology Research Alliance; CRF = Case Report Form; *DSUR=development safety update report; HA=Health Authority;* ICF = Informed Consent Form; JuMBO = Juvenile arthritis Methotrexate/Biologics long-term Observation; *PBRER= periodic benefit-risk evaluation report.*

## 5.2 RATIONALE FOR STUDY DESIGN

TCZ (IV or SC) alone or in combination with methotrexate has been approved for the treatment of patients 2 years of age or older with active pJIA in the United States and the European Union. This study is designed to allow for collection and analysis of aggregate and some patient-level safety and effectiveness data from patients with pJIA in a real-world setting. The international setting will allow for a geographically diverse population, including the United States and the European Union. The data collection period of a maximum of 5 years for patients receiving TCZ (IV or SC) will allow for long-term efficacy and safety assessment and collection of data on growth and development in patients enrolled in the feeder registries.

## 5.3 PATIENT POPULATION

Patients enrolled in the feeder registries must meet all of the following criteria for inclusion in this study:

- Diagnosis of pJIA, defined according to ILAR classification (Petty et al. 2004), and in line with the licensed indications in the United States and the European Union:

  Patients with RF-positive pJIA

  Patients with RF-negative pJIA

  Patients with eoJIA

- Initiation of treatment with TCZ (IV or SC) or a comparator biologic

  The TCZ group will include patients with no previous exposure to TCZ (IV or SC). The comparator biologic group will include patients with no previous exposure to that specific comparator biologic.

- Age ≤17 years at the time of initiation of treatment with TCZ (IV or SC) or a comparator biologic

## 5.4 DOSAGE, ADMINISTRATION, AND COMPLIANCE

Dosing and treatment duration for TCZ IV or SC and the comparator biologic are at the discretion of the patient's physician in accordance with local clinical practice and local labeling.

## 5.5 PATIENT ENROLLMENT AND COHORT ASSIGNMENT

There is no protocol-mandated treatment assignment in the feeder registries, and the decision to prescribe TCZ (IV or SC) or a non-TCZ biologic comparator will be made by a physician and patient without regard to potential participation. Patients meeting the inclusion criteria and providing consent to the registry will be allocated to one of the two groups, TCZ or non-TCZ comparator, based on physician-assigned treatment.

As agreed with the FDA, to ensure the two treatment cohorts are balanced with respect to geographic region and timing of enrollment, patients will only be enrolled if a TCZ (IV or SC) patient can be matched to a non-TCZ comparator patient based firstly on

geographical region and then on calendar period (must have newly initiated therapy with TCZ [IV or SC] and non-TCZ comparator within a period of 3 months on either side of the treatment initiation date). This will ensure that matched patients are enrolled into their respective treatment cohorts during a defined period where prescribing practices will not differ.

Patients enrolled in the comparator cohort who subsequently switch to treatment with TCZ (IV or SC) can be re-enrolled in the TCZ cohort provided the TCZ cohort is still open for enrollment, they meet all the inclusion criteria, and they can be matched to a comparator cohort patient in the same manner as all other patients being enrolled into the TCZ cohort. Hence, a patient can contribute data to both cohorts. However, if the patient subsequently switches treatment back to the original comparator biologic or a different comparator biologic, they will not be re-enrolled into the comparator cohort.

Similarly, patients enrolled into the TCZ cohort who subsequently switch to a comparator biologic can be re-enrolled into the comparator cohort provided the cohort is still open for enrollment, they meet all the inclusion criteria, and they are the best match for an enrolling TCZ cohort patient. Otherwise, they will only contribute to the TCZ cohort. Patients originally enrolling into the TCZ cohort, then enrolling into the comparator cohort, who then switch treatment back to TCZ (IV or SC), cannot re-enroll into the TCZ cohort.

Patients can only enroll into each cohort once. Details of the geographic regions used for each registry are described in the Statistical Analysis Plan.

Note that for the CARRA registry, over-enrollment occurred within the non-TCZ comparator arm during the first year of enrollment. To adjust for this disparate enrollment rate, the TCZ patients already enrolled during this period will be retrospectively matched at random (if greater than one match exists) to non-TCZ comparator patients firstly by geographical region and time period (newly initiated therapy with non-TCZ comparator within a period of 3 months on either side of the treatment initiation date). Any non-TCZ comparator patients without a match will not participate in this study, unless a match is obtained at a later date.

The 5-year report will state that the concurrent enrollment model was applied retrospectively for patients from the CARRA registry (where comparator patients were initially recruited faster than TCZ patients), and prospectively for all patients enrolled into the study from all participating registries.

Data handling conventions for patients who switch, discontinue, or interrupt treatment with the TCZ (IV or SC) or a non-TCZ comparator are described in the Statistical Analysis Plan.

## 5.6 PRIMARY OUTCOME MEASURES

The outcome measures for the study are as follows.

- Rate of serious adverse events
- Rates of adverse events in the following categories of special interest:
    - Serious infections
    - Serious cardiovascular events
    - Serious and non-serious malignancies
    - Serious gastrointestinal perforations
    - Serious and non-serious uveitis events
- Rate and treatment outcome of uveitis
- Growth patterns (relative to age-specific standards for height and weight)
- Development patterns (via self-reported or examined Tanner staging)
- JADAS-10

Further details on the data collection, data analysis, and reporting can be found in the Statistical Analysis Plan.

## 5.7 ADVERSE EVENT REPORTING

The study utilizes secondary data collection, therefore there is no requirement to collect or report Individual Case Safety Reports. However, safety reporting responsibilities will be documented in agreements with the feeder registries.

Roche has confirmed that the feeder registries will report the following adverse events:

- Infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious])

## 5.8 DATA COLLECTION AND MANAGEMENT

The observation period for this study is defined as a maximum of 5 years for all patients.

All data included in this study will be obtained from active feeder registries. Patient data will be collected by the feeder registries via paper or electronic Case Report Forms. The data collection for this study is suggested to start at baseline and continue every 6 months thereafter or according to local practice and upon completion of the study or upon early termination from the feeder registry. Data collection may be supplemented by extracting data recorded prior to baseline and between patient visits, according to feeder registry practices.

The feeder registries will be responsible for management of the data they collect, including quality checking of the individual data points. Accurate and reliable data

collection will be ensured by each feeder registry's standard processes for data collection and verification.

Aggregate data reports will be transferred to Roche at annual intervals by the feeder registries, and some patient-level data will be transferred at the 5-year time point, as specified in the Statistical Analysis Plan.

## 5.9 MONITORING OF FEEDER REGISTRY PROCESSES

Roche will monitor the processes at the feeder registries on a periodic basis to ensure the collection and reporting of data to Roche meets international standards for data quality and patient safety.

## 5.10 FEEDER REGISTRY REPLACEMENT

Roche has the right to replace a feeder registry at any time. Reasons for replacing a feeder registry and respective sites may include, but are not limited to, the following:

- Excessively slow recruitment
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPPs) or any other pertinent local laws or guidelines

## 5.11 STUDY SIZE

Aggregate and some patient-level data will be collected from a sample size of *approximately 300* patients with pJIA receiving TCZ (IV or SC), and another *approximately 300* patients with pJIA receiving a comparator biologic. Patients receiving TCZ (IV or SC) or a comparator biologic will be enrolled in the feeder registries and followed for 5 years to allow for detection of serious adverse events (and events of special interest) over long-term observation and to enable observation of efficacy, growth and development patterns over this extended period of time.

*Based on data snapshots for the CARRA (15 July 2019) and BiKeR (3 June 2019) registries, it is estimated that approximately 30% of the patients will discontinue TCZ (IV or SC) in their first year of treatment, with approximately 15% of the remaining patients discontinuing TCZ (IV or SC) treatment in each subsequent year, and with 2% of patients per year lost to follow up. These revised assumptions, along with an enrollment of approximately 300 patients treated with TCZ (IV or SC), provides a revised estimate of 99 patients treated with TCZ (33%) with data for 5 years of TCZ (IV or SC) therapy, and 270 patients treated with TCZ (90%) with 5 years of follow-up in the study (either on or off TCZ). Hence, the total number of patients with 5 years of follow-up will be higher than previously predicted (270 vs. 237 patients); however, a lower number of patients will have been exposed to TCZ for over 1 year (206 vs. 324 patients). The reduced number of patients exposed to TCZ (IV or SC) is due mainly to a higher rate of TCZ withdrawal than previously expected.*

*With approximately 300 TCZ-treated (IV or SC) patients enrolled, the estimate of total exposure in patient years for the TCZ arm is predicted to be 840 patient years exposure to TCZ, with a total exposure of 1425 patient years, assuming patients contribute half a year of exposure on average in the year they are lost to follow-up/discontinue TCZ (IV or SC) treatment. This compares favorably to the figures stated in the previous versions of the protocol (where a* sample size of 400 patients in the TCZ group *would* result in *approximately* 240 patients at the end of 5 years, and up to approximately 1200 patient years in total for the study).

*For the evaluation of* growth *and development, previous versions of the protocol expected to* include approximately 240 patients *treated with* TCZ *(IV or SC)* aged ≤11 years, *with approximately* 100 of these patients expected to complete the 5-year study, allowing for assessment of long-term growth patterns through adulthood. *In the CARRA and BiKeR data snapshots, 114 (50%) of the 230 patients treated with TCZ enrolled to date were <11 years. Therefore, it is now predicted that approximately 150 patients will be <11 years. With 90% of these patients completing the 5-year follow-up, this would provide approximately 135 patients for the long-term evaluation of growth and development. This compares favorably to the previously estimated figure of 100 patients.*

*In order to evaluate of the effectiveness of the 10 mg/kg IV TCZ Q4W regimen for* patients *who weigh <*30 kg, *the study was originally expected to* include approximately 150 patients in the TCZ group *weighing <*30 kg. However, as a consequence of the subsequent approval of TCZ SC for the treatment of pJIA in the European Union and United States in 2018, the number of patients on TCZ IV was expected to be reduced by 30% to 50%. *Consequently, the expected number of patients on the 10 mg/kg IV TCZ Q4W regimen was expected to be reduced from 150 patients to 50–75 patients. Based on the CARRA and BiKeR data snapshots, of the 230 patients enrolled, 45 patients (20%) weighed <30 kg at enrollment, and 40 of these 45 patients (89%) were on the 10 mg/kg IV Q4W regimen. Therefore, of the next 70 patients enrolled (to give 300 in total in the TCZ group as expected under the current version of the protocol), approximately 14 patients (20%) are expected to weigh <30 kg. Based on the snapshot data, the majority of these patients are expected to be on IV rather than SC, providing at least 50 of 300 patients treated with TCZ on the 10 mg/kg IV Q4W regimen with this protocol amendment. Although this is lower than initially predicted with the original protocol, it is considered adequate, given the longer-term efficacy reported for Study WA19977 (CHERISH), which showed that in general, patients weighing <30 kg on the 10 mg/kg IV Q4W regimen had a trend toward better efficacy responses through the end of the study at Week 104 than those on the 8 mg/kg IV Q4W regimen, including JIA ACR 30/50/70/90, JADAS-71, inactive disease, and clinical remission (WA19977 Week 104 Clinical Study Report; available upon request).*

## 5.12 ANALYSIS OF OUTCOME MEASURES

Descriptive summary analyses will be used to characterize baseline demographics (which may include, but are not limited to, family income, geographic region, sex, race, ethnicity, and age), medical history (which may include, but is not limited to, comorbidities, disease phenotype, previous biologic treatment, disease activity, severity, and duration), medications (which may include, but are not limited to, methotrexate, corticosteroids, and growth hormone), growth (height and weight), development (self-reported or examined Tanner staging).

Incidence rates, with 95% confidence intervals, will be provided for serious adverse events. In addition, the number of serious adverse events and percentage of patients with at least one event will be summarized by Medical Dictionary for Regulatory Affairs System Organ Class and Preferred Term. Rates of all serious adverse events and rates of adverse events in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious]) will be calculated on the basis of the drug exposure period for both the TCZ group and the comparator group (i.e., patients receiving a comparator biologic). Rates of selected events that could be potentially associated with prior drug exposure (including cardiovascular events and malignancies) will also be calculated for both the TCZ group and the comparator group; events occurring any time during follow-up (including the period after treatment discontinuation) would be included in incidence rate calculations. Incidence rates of serious adverse events and 95% confidence intervals will be presented for the TCZ group and the comparator group at 5 years.

The height standard deviation scores will be summarized descriptively over time by treatment group. The data for development patterns will be summarized by gender for each treatment group. The rate of uveitis and description of treatment outcome will be summarized. JADAS-10 will be summarized over time. The Statistical Analysis Plan outlines which analyses will be performed for all patients enrolled in the study, the TCZ group, the comparator group, the subgroups of patients with a baseline body weight of $<30$ kg or $\geq 30$ kg, and the subgroups of RF-positive and RF-negative patients. JADAS-10 will also be summarized for patients in the TCZ group with a baseline bodyweight of $<30$ kg.

Patients who switch therapy or discontinue therapy during the observation period will continue to be followed to allow for long-term safety assessment of serious adverse events and adverse events in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious]). These data will be included in the calculation of incidence rates of events associated with prior treatment exposure. After all patients have completed up to 5 years of treatment, data from the TCZ group will be presented with data from the comparator group.

Annual reports based on summary reports provided by each individual feeder registry will be produced. A 5-year report of the overall summary data combining data from the feeder registries will also be produced. No formal hypothesis tests will be conducted.

A model-based approach using combined individual patient data from all registries adjusting for confounders will be applied to estimate the risk of adverse events for selected events.

Full details of planned statistical summaries will be specified in a separate Statistical Analysis Plan.

### 5.13 LIMITATIONS OF THE RESEARCH METHOD

Because patients are not randomized to treatment, patients in the TCZ group and patients in the comparator group may differ with regard to baseline characteristics. Data on treatment outcome for uveitis and self-reported or examined Tanner staging may not be available for all patients. Comparison of the safety and efficacy between the two groups may be subject to bias. The long duration of study follow-up may result in a sizable loss of study participants, which could result in under-reporting of safety events. To minimize loss of study participants, the feeder registries will be advised to instruct their sites to encourage all patients, including those who discontinue TCZ or the comparator biologic or switch to other therapies during the study, to remain in the feeder registry to maximize data collection.

## 6. PROTECTION OF HUMAN SUBJECTS

### 6.1 COMPLIANCE WITH LAWS AND REGULATIONS

The feeder registries will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted (see European Union guideline on Good Pharmacovigilance Practices).

The feeder registries will comply with national, international, and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

### 6.2 CONFIDENTIALITY

Roche will receive aggregate and some patient data from each feeder registry. Only anonymized patient data will be transmitted.

## 7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study may be published or presented at scientific meetings. If this is foreseen, the feeder registries and feeder registry investigators agree to submit all

manuscripts or abstracts to Roche prior to submission. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the feeder registry investigators.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the feeder registry investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from the study will become and remain the exclusive and unburdened property of Roche, except when agreed otherwise.

## 8. REFERENCES

Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.