F. HOFFMANN-LA ROCHE LTD

CLINICAL STUDY PROTOCOL

NUMBER ML28747

RO 4877533

TOCILIZUMAB

FINAL

Sponsor: **F. HOFFMANN-LA ROCHE LTD**

Grenzacherstrasse 124,

4070 Basel,

Switzerland

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PROTOCOL APPROVAL

Protocol number / Version: ML28747 v. 3

Date: See last date electronic signature statement below.

Protocol approved by: See last date electronic signature statement below.

HISTORY OF AMENDMENT TO PROTOCOL, VERSION 2.0: JUSTIFICATION

The ML28747 protocol was amended to detail section reports of adverse events , adverse events of special interest and serious adverse events .

Other minor changes were made to improve the clarity and uniformity of texts.

HISTORY OF AMENDMENT TO PROTOCOL, VERSION 2.0
SUMMARY OF CHANGES

PROTOCOL BODY

The body of the protocol was updated to reflect the changes made to the protocol , as appropriate.

-Added Section 5.5.1 :

5.5.1 Patient-Reported Outcome Data (PRO data)

AE reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible AE are identified during site review of the PRO data, the investigator will determine whether the criteria for an AE have been met and, if so, will report the event on the AE eCRF.

-Made a clarification on related no serious adverse events:

7.1.1.2 Relation to Medication - Adverse Event

The investigator evaluated the causal relationship between the study medication and AE as Yes or No.
To assess the relationship to Yes, the following criteria will be considered:

- There is a reasonable temporal association between AE and the administration of medication.
- The AE may or may not have been produced by the patient's clinical status, toxic or environmental factors, or other forms of treatment administered.
- The AE exhibits a known response pattern to the suspected medication.

- The AE disappears or lessens after suspension or dose reduction.
- The AE reappears with resumption.

To evaluate the relationship as No, the following criteria will be considered:

- AE does not follow a reasonable temporal sequence in the administration of medication.
- The AE could easily have been produced by the patient's clinical status, toxic or environmental factors, or other forms of treatment administered.
- The AE does not follow a known pattern of response to the alleged medication.
- The AE does not reappear or worsen when administration is resumed.

All no serious adverse event related with medicinal product included for which the timeline is not 24 hours but 30 calendar days.

-Made a clarification of hepatic events and Suspected transmission of an infectious agent by the study drug:

7.1.1.3 Special Interest Adverse Events

AEs of special interest include:

• Infections (including opportunistic infections);
• Myocardial infarction / acute coronary syndrome;
• Gastrointestinal perforations (GI) and related events;
• Malignant tumors;
• Hypersensitivity reactions (including reactions at the injection site);
• Demyelinating disorders;
• Cerebrovascular accident;
• Bleeding events.
• Hepatic events (including cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law).
• Suspected transmission of an infectious agent by the study drug, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.

-Made a clarification of “severe” and “serious”:

7.1.1.4 Serious Adverse Events (Immediate Notification to Roche)

SAE is a great experience which carries a risk, contraindication, side effects or significant caution. It is any AE that at any dose combines at least one of the following criteria:

- It is fatal; (** NOTE leads to death, death is an outcome, not an event)
- Life Threatening. NOTE: The term "Life-Threatening" refers to an event in which the patient has imminent risk of death at the time of the event, does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of hospitalization.
- Leads to disability / persistent or significant disability.
- Is a congenital anomaly / birth defect.

- Is medical significant or requires intervention to prevent any of the aforementioned consequences

**** The term sudden death will be used only when the cause is cardiac according to standard definition. The terms death and sudden death have undeniably different meanings and should not be used interchangeably.**

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).
Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

-Added the following sections:

7.2.4Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ the ULN) in combination with either an elevated total bilirubin ($>2\times$ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ the ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 7.1.1.3 and Section 7.2.3).

7.2.5

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche to the pharmacovigilance Unit.

7.2.5.1 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within corresponds to time needed to eliminate drug (□5 half-lives) plus 74 days (a spermatogenesis cycle)after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted to Safety Unit. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient

exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF and to Safety Unit with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.2.5.2 Abortions

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the AE eCRF, and reported to the Sponsor to the pharmacovigilance Unit immediately (i.e., no more than 24 hours after learning of the event). Any abortion should be recorded on Clinical Trial Pregnancy Reporting form and submitted to Roche Safety Unit.

7.2.5.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the drug under observation or the female partner of a male patient exposed to the drug under observation should be classified as an SAE, recorded on the AE eCRF, and reported to the Sponsor to the pharmacovigilance Unit immediately (i.e., no more than 24 hours after learning of the event)

7.3.8.1 Infusion-Related or *Injection Reactions*

AEs that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion ***or*** injection should be captured as a diagnosis (e.g., "infusion-related reaction" ***or*** "injection-site reaction" ***or*** "anaphylactic reaction") on the AE eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction ***or*** Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the AE eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction ***or*** Injection Reaction eCRF.

7.4 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error, or any other incorrect administration of drug under observation should be noted on the Drug Administration eCRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error, or occupational exposure reports must be forwarded to the sponsor with or without an AE.

Reports with or without an AE should be forwarded to the Sponsor to the pharmacovigilance Unit as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the Sponsor to the pharmacovigilance Unit immediately (i.e., no more than 24 hours after learning of the event,).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a drug under observation means an exposure to a drug under observation as a result of one's professional or non-professional occupation.

7.5 Adverse Events Occurring Secondary to Other Events

In general, AEs that are secondary to other events should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the AE eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

7.6 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the AE eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the AE eCRF. If the event becomes serious, it should be reported to the Sponsor to the pharmacovigilance Unit immediately (no more than 24 hours after learning that the event became serious). The AE eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the AE eCRF.

7.7 Lack of Therapeutic Efficacy or Worsening of Arthritis Rheumathoide

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on local assessment of disease (i.e.: DAS28 worsening). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective

criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

7.8 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 7.1.1.4), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

– The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

– The patient has not suffered an AE.

The following hospitalization scenarios are not considered to be SAEs but should be reported as AEs instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

7.9 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the AE eCRF.

7.10 Follow-Up of Patients after Adverse Events

7.10.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate SDV.

All pregnancies reported during the study should be followed until pregnancy outcome.

7.10.2 Sponsor Follow-Up

For SAEs, non-serious AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

7.11 Post-Study Adverse Events

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent AEs that could be related or not to the drug under observation. The investigator/physician should notify the Sponsor to the pharmacovigilance Unit of any death, SAE, AE or non-serious AE of special interest related to the medicinal product occurring at any time after a patient has discontinued study participation. The Sponsor to the pharmacovigilance Unit should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study. The investigator does not need to actively monitor patients for AEs once the trial has ended.

The investigator should report these events directly to Roche, by scanning and emailing the Serious Adverse Event / Adverse Event of Special Interest Reporting Form/Adverse Event Form using the email address provided to investigators.

-Removes the section Annual security reports:

12.3 Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

In the member states of EEA, the Sponsor shall submit to the Competent Authority and the IEC the protocol and all accompanying material that has been provided to the patient. The accompanying material may include an information booklet for patients, descriptions of the study used to obtain informed consent and the terms of any compensation that is offered to the patient as well as any advertising which is developed for the clinical study.

Before starting the study, the investigator must obtain a letter or certificate of approval (mentioning the protocol number and title) of the IEC / IRB, specifying the date on which the committee met and granted approval. This applies whenever an amendment / post protocol is made.

Any modification to the protocol, informed consent or material handed to the patient after the approval of IEC / IRB should also be delivered by the Sponsor in the EEA member countries, according to local procedures and regulatory requirements.

Where there is no local committee, the investigator must submit the protocol to a regional committee. If there is no regional committee, Roche will help the investigator in submitting the protocol to the European Ethics Committee.

~~Roche also will submit an Annual Safety Report once a year to the IEC and Competent Authorities in accordance with local regulatory requirements and time limits in effect in each country participating in the study.~~