Online Supplementary Appendix 1: Additional protocol information

PROTOCOL V0.1; 7 NOVEMBER 2016

Protocol amendment

Any protocol amendments will be prepared by F. Hoffmann-La Roche, Ltd. (the Sponsor). Protocol amendments will be submitted to the Institutional Review Board/Ethics Committee (IRB/EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval will be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in Medical Monitor or contact information).

Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the trial through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained in this trial is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorisation for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician, or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data quality assurance

The Sponsor will supply electronic case report form (eCRF) specifications for this trial. A clinical research organisation (CRO) will be responsible for data management in this trial, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. The Sponsor will perform oversight of the data management in this trial, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the trial data will be consistent with the CRO's standard procedures.

Patient-reported outcomes data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

Electronic case report forms

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

After the end of the adverse-event–reporting period (defined as 28 days after the last dose of trial treatment), all deaths, regardless of cause, will be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior trial treatment, the event will be reported through use of the Adverse Event eCRF.

At the end of the trial, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the trial records. Acknowledgement of receipt of the compact disc is required.

Source data documentation

Trial monitors will perform ongoing source data verification to confirm that critical protocol data entered into the eCRFs by authorised site personnel are accurate, complete and verifiable from source documents.

Before trial initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (ie, no prior written or electronic record of the data) and considered source data. Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the pre-determined policy for retention of records (see below).

To facilitate source data verification, the investigators and institutions must provide the Sponsor with direct access to applicable source documents and reports for trial-related

monitoring, Sponsor audits and IRB/EC review. The trial site must also allow inspection by applicable health authorities.

Use of computerised systems

When clinical observations are entered directly into a trial site's computerised medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerised systems used in clinical research. An acceptable computerised data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, the name of the person making the change and the date of the change.

Retention of records

Records and documents pertaining to the conduct of this trial and the distribution of the investigational medicinal product, including eCRFs, Informed Consent Forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the trial or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Data dissemination

Regardless of the trial outcome, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The results of this trial may be published or presented at scientific congresses. For all clinical trials in patients involving an investigational medicinal product (IMP) for which a marketing authorisation application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorisation application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre trials only in their entirety and not as individual centre 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 trial in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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