To:

All Member States participating in EFC17504

23rd January 2024

Product Code/Name: SAR441344 / Frexalimab

Protocol Code: EFC17504

Protocol Title: A randomized, double-blind, Phase 3 study comparing efficacy and safety of frexalimab (SAR441344) to placebo in adult participants with nonrelapsing secondary progressive multiple sclerosis

Universal trial number: U1111-1280-7114

EU trial number: 2023-504359-29

Subject: Clinical Trial Application - Request for Initial authorization

Dear Madam, Dear Sir,

Sanofi-Aventis Recherche & Développement hereby submits a Clinical Trial Application for the Clinical Study EFC17504

EFC17504 is a Phase III randomized, double-blind, 2-arm, placebo-controlled, parallel group, multicenter study, in adult participants with non-relapsing secondary progressive form of Multiple Sclerosis.

The purpose of this study is to assess the efficacy of frexalimab in delaying disability progression, its safety and tolerability in participants.

We propose Czech Republic as the Reporting Member State.

The Sponsor wishes to highlight that another frexalimab Phase III study (EFC17919 [EU CTR number 2023-504358-36-00]) has been submitted prior to the hereby application. The Sponsor therefore proposes to request the same Reporting Member State (Czech Republic) for both studies for optimization of review and future maintenance.

For the same purpose, the Sponsor would like to point out that in terms of the Quality information, the IMPD Quality provided as part of this application for study EFC17504 is the same as the one that has been provided for the EFC17919 application. The exception being that study EFC17919 uses a comparator and comparator placebo, whereas EFC17504 does not.

The following Countries are proposed to take part in the study:

- Bulgaria
- Belgium
- Czech Republic
- Germany
- France
- Greece
- Hungary
- Italy
- Netherlands
- Poland
- Portugal
- Spain
- Sweden

The anticipated date of the next DSUR submission is 12-Jan-2024

We confirm that the contact details of the main contact of the sponsor are included in the patient card (as per the Annex VI of the Regulation, paragraph 3 of section A.1).

For administrative information, please see Administrative information.

For any additional information, please see Specificities.

Should you have any queries on the enclosed, please do not hesitate to contact us

Yours sincerely,

Sanofi-Aventis Research & Development

Administrative information

Information		**Location of the Information in the Application Dossier**
Proposed Reporting Member State	Czech Republic	Not Applicable
Specific features of the clinical trial population	☐ Subjects not able to give informed consent ☐ Minors ☐ Pregnant or breastfeeding women ☒ None of the above	Please refer to Structure Data in the Part I \ Trial details \ Trial information \ Population of trial subjects
Does the clinical trial involve the first administration of a new active substance to humans?	☐ Yes ☒ No	Not Applicable
Has a scientific advice relating to the clinical trial or the investigational medicinal product SAR441344 / Frexalimab been given by the Agency, a Member State or a third country?	☒ Yes ☐ No	Please refer to Structure Data in the Part I \ Trial details \ Scientific advice and Paediatric Investigation Plan (PIP)
Is the clinical trial part or will it be part of a Paediatric Investigation Plan (PIP)?	☐ Yes ☒ No	Please refer to Structure Data in the Part I \ Trial details \ Scientific advice and Paediatric Investigation Plan (PIP)
Has the investigational medicinal product SAR441344 / Frexalimab obtained an orphan designation?	☐ Yes ☒ No	Please refer to Structure Data in the Part I \ Products \ SAR441344 / Frexalimab \ Orphan Designation
Is the clinical trial considered by the sponsor to be a low-intervention clinical trial?	☐ Yes ☒ No	Please refer to Structure Data in the Part I \ Trial details \ Trial information \ Trial Category
Does the methodology of the clinical trial require that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial? If Yes, will the informed consent be obtained by simplified means?	☐ Yes ☒ No ☐ Yes ☐ No	

The Investigational Medicinal Product in this clinical study is:

Investigational Medicinal Product	Regulatory status	Reference Safety Information localisation	Additional information
SAR441344 / Frexalimab	☐ Approved in the EU ☒ Not Approved in the EU	Section 8 (Determination of expectedness and the table of expected adverse drug reactions) of the Investigator's Brochure Edition 5 dated 17-Apr-2023	Is the IMP a: - narcotic: ☐ Yes ; ☒ No - psychotropic: ☐ Yes ; ☒ No -radiopharmaceutical: ☐ Yes ; ☒ No (Please refer to Structure Data in the Part I \ Products \ SAR441344 / Frexalimab \ Product characteristics) Does the IMP consist of or contain a genetically-modified organism or organisms? ☐ Yes ; ☒ No (Please refer to Structure Data in the Part I \ Products \ SAR441344 / Frexalimab \ Advanced Therapy Medicinal Product)

The auxiliary medicinal products in this clinical study are:

Auxiliary medicinal product	Regulatory status	Additional information
MRI contrast- enhancing Preparations (ATC code: V08CA)	☒ Approved in the EU ☐ Not Approved in the EU	Sourcing by the site/patient for all countries. Sourcing by/on behalf of the Sponsor: No

No medical devices are being investigated as part of the clinical trial. The in vitro diagnostic medical devices which are to be included in this clinical trial but which are not part of the investigational medicinal product or products are:

Medical device	Additional Information
Activated Partial Thromboplastin Time – CLOT DETECTION	This test is CE-marked for the intended use.
anti-Hepatitis B Surface Antigen 2 (aHBs2) - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Anti-Mitochondrial Antibody – INDIRECT FLUORESCENT ANTIBODY	This test is CE-marked for the intended use.
Antinuclear Antibody (ANA) – INDIRECT FLUORESCENT ANTIBODY	This test is CE-marked for the intended use.
Anti-Smooth Muscle Antibody – INDIRECT FLUORESCENT ANTIBODY	This test is CE-marked for the intended use.
Beta hCG - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Chemistry Panel – VARIES BY ANALYTE	This test is CE-marked for the intended use.
Cytomegalovirus IgM - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
D-Dimer – COAGULATION ANALYZER	This test is CE-marked for the intended use.

Double Stranded DNA Antibodies, IgG – INDIRECT FLUORESCENT ANTIBODY	This test is CE-marked for the intended use.
Epstein-Barr VCA IgG- CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Epstein-Barr VCA IgM - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Ferritin - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Follicle Stimulating Hormone (FSH) - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Full liver panel – VARIES BY ANALYTE	This test is CE-marked for the intended use.
Gilbert Syndrome Screening for UGT1A1*28 (rs8175347) polymorphism – RT-PCR	This test is CE-marked for the intended use.
Glucose – CHEMISTRY COBAS 701/702	This test is CE-marked for the intended use.
HBV DNA – RT-PCR COBAS 6800	This test is CE-marked for the intended use.
HCV RNA – RT-PCR COBAS 680	This test is CE-marked for the intended use.
Hematology Differential – LIGHT SCATTERING	This test is CE-marked for the intended use.
Hematology Hemogram Panel – VARIES BY ANALYTE	This test is CE-marked for the intended use.
Hepatitis A IgM Antibody - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Hepatitis B Core IgM Antibody - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Hepatitis B Core Total - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Hepatitis B Surface Antigen II - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Hepatitis C Virus Antibody - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Hepatitis E IgM Antibody – ENZYME IMMUNOASSAY	This test is CE-marked for the intended use.
Herpes Simplex Virus Type 1 IgG Antibody - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Herpes Simplex Virus Type 2 IgG Antibody - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Herpes Simplex Virus Type 1+2 IgM Antibody - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
HIV 1/2 Ag/Ab Combo (CHIV) - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
HIV-1 Antibody Supplemental, Geenius - IMMUNOCHROMATOGRAPHIC	This test is CE-marked for the intended use.
HIV-1 RNA – RT-PCR	This test is CE-marked for the intended use.
HIV-2 Antibody Supplemental – IMMUNOCHROMATOGRAPHIC	This test is CE-marked for the intended use.
HIV-2 RNA – RT-PCR	This test is CE-marked for the intended use.
Immunoglobulin G – CHEMISTRY COBAS C 701/702	This test is CE-marked for the intended use.
Immunoglobulin M – CHEMISTRY COBAS C 701/702	This test is CE-marked for the intended use.
International Normalized Ratio – CLOT DETECTION	This test is CE-marked for the intended use.
Liver Kidney Microsome Antibody – ENZYME IMMUNOASSAY	This test is CE-marked for the intended use.
Polyomavirus JC – RT PCR	This testing will be performed at a laboratory within Europe that qualifies for in-house testing exemption under Article 5(5) of EU IVDR.
Prothrombin Time – CLOT DETECTION	This test is CE-marked for the intended use.
QuantiFERON-TB Gold Plus – ENZYME IMMUNOASSAY	This test is CE-marked for the intended use.
Reticulocyte Count – FLOW CYTOMETRY	This test is CE-marked for the intended use.
SARS-CoV2 Qualitative – RT-PCR	This test is CE-marked for the intended use.
Total Iron – CHEMISTRY COBAS C 701/702	This test is CE-marked for the intended use.
Total Iron Binding Capacity - CALCULATION	This test is CE-marked for the intended use.

Toxoplasma Antibody IgG - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Toxoplasma Antibody IgM - CHEMILUMINESCENCE	This test is CE-marked for the intended use.
Unsaturated Iron-Binding Capacity – CHEMISTRY COBAS C701/702	This test is CE-marked for the intended use.
Urinalysis, Dipstick – REFLECTANCE PHOTOMETRY	This test is CE-marked for the intended use.
Urinalysis, Microscopic – MICROSCOPIC ANALYZER	This test is CE-marked for the intended use.

Specificities

Local pre-Scientific Advice meeting according to KBPV has not taken place in Germany

Radiation protection assessment by Ethics Committee is not required in Germany

The proposed Ethics Committee for Italy is:

Comitato Etico Territoriale della Regione Siciliana

email: cetsicilia@policlinico.pa.it

Stamp duty virtually paid pursuant to Art. 15 of DPR 642 of 26.10.1972, authorization no. 267351 of 9.11.2020 issued by the Revenue Agency, provincial direction of Milan 2

The proposed Ethics Committee for Netherlands is:

MREC Z, mevrouw mr. S.A.E., Vanhouwe, PO Box 5500, 6130 MB Sittard, The Netherlands, +31 88 459 01 2, metc@zuyderland.nl

The proposed Ethics Committee for Spain is:

CEIm Parc, TauliParx, Taulu, 1-Edifici Santa Fe, ala izquierda planta 2a, localided: Sadabell CP: 08208

REec user: es-reg-estudiosclinicos@sanofi.com