Better Health, Brighter Future

Date: 28 Feb 2024

EU Trial Number:	2023-504773-20-00
Protocol code:	Vedolizumab-3041
Protocol title:	An Open-label Single-Arm Phase 3 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Vedolizumab Intravenous in the Treatment of Pediatric Subjects With Active Chronic Pouchitis
Sponsor:	Takeda Development Center Americas, Inc
Subject:	Request for Authorization of an Initial Clinical Trial Application under Regulation (EU) No 536/2014

Dear Madam, Dear Sir,

Takeda Development Center Americas, Inc, as sponsor of the above clinical trial, hereby submits a request for Clinical Trial Authorisation. Please be informed that as per the Sponsor's decision, the abbreviated EU Clinical Trial number (EU CT number) is used on all documents uploaded to CTIS, i.e. the last two digits are not mentioned. The complete EU CT number will be reported only in the cover letters moving forward.

The documents in this submission have been prepared in accordance with the European Union Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

Study Details:

This is a phase 3 open-label single-arm study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and immunogenicity of vedolizumab intravenous (IV) administered over a 34-week treatment period as treatment for active chronic pouchitis in pediatric subjects aged 2 to 17 years, inclusive, who have had an inadequate response with or have lost response to or are intolerant to antibiotic therapy.

Takeda Development Center Americas Inc.

95 Hayden Avenue, Lexington, 02421-7942 United States

The study will be conducted in approximately 20 sites globally.

Target population

Approximately 30 subjects aged 2 to 17 years inclusive at the time of screening and first dose, who have active chronic pouchitis, will be enrolled to achieve at least 20 evaluable pediatric subjects for the primary analysis.

Orphan Status:

The investigational product does not have orphan designation in the European Union (EU) for the indication under investigation.

Scientific Advice:

Scientific advice relating to the clinical trial/IMP has not been sought with the European Medicines Agency (EMA) and Member States Concerned, nor the competent authority of a third country.

Paediatric Investigation Plan:

The clinical trial is part of a Paediatric Investigation Plan (PIP) per Title II, Chapter 3, of Regulation (EC) No 1901/2006,PIP Decision number P/0382/2023, for which a link is included with this application: European Medicines Agency decision P/0382/2023 of 7 September 2023 on the acceptance of a modification of an agreed paediatric investigation plan for vedolizumab (Entyvio), (EMEA-000645-PIP04-20-M02) (europa.eu) .

Investigational Medicinal Product(s) and Auxiliary Medicinal Product(s):

The following Investigational Medicinal Product(s) (IMP(s)) is included in the clinical trial:

Product name	*Regulatory status*	*Reference Safety Information*	*Additional information*
Vedolizumab IV	Authorised for adults	IB Ed 28 dated 14-Nov-2023	Not Applicable

Investigational Medicinal Product (IMP):

The drug substance, vedolizumab, is a humanized immunoglobulin G1 monoclonal antibody directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to gastrointestinal (GI) mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa. Vedolizumab binds the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator.

Vedolizumab drug substance monoclonal antibody is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology (it is not a genetically modified organism).

Vedolizumab drug product has Marketing Authorisation in the EU (and multiple other countries worldwide) under the invented name of Entyvio 300 mg powder for concentrate for solution for infusion.

Takeda will supply the study sites with drug product vedolizumab IV 300 mg/vial, powder for concentrate for solution for infusion, for single use in a 20 mL vial. For the purpose of this clinical trial, naked drug product vials, manufactured according to the approved commercial process, will be labeled for clinical trial use in accordance with the EU good manufacturing practices documentation and kitted for distribution to study sites. The composition of the drug product is not altered during the labeling and kitting procedure.

Importation and responsibility for final Qualified Person (QP) release for sites in the EU lies with Almac Clinical Services UK 9 Charlestown Road, Seagoe Industrial Estate, Craigavon, (Northern Ireland), BT63 5PW, UK.

Fisher Clinical Services sites that are listed in the Simplified IMPD, 2.1.P.3.1 Manufacturer(s) section will not be involved in this study.

The required manufacturer / importer authorizations and the trial specific EU QP Good Manufacturing Practice (GMP) declaration for manufacturing site and operations supporting the clinical trial application are enclosed.

The following Auxiliary Medicinal Product(s) (AxMP(s)) are included in the clinical trial:

Product name	*Regulatory status*	*Additional information*
Ciprofloxacin ATC code: J01MA02	Authorised	Not Applicable
Metronidazole ATC code: P01AB01	Authorised	Not Applicable
Vancomycin ATC code: A07AA09	Authorised	Not Applicable
Amoxicillin clavulanate ATC code: J01CR02	Authorised	Not Applicable
Rifaximin ATC code: A07AA11	Authorised	Not Applicable

The AxMPs will be sourced locally by the study sites, hence no additional documentation is included as part of this application, except for the representative Summary of Product Characteristics (SmPC).

None of the investigational medicinal products [or auxiliary medicinal products] in this clinical trial are a narcotic, psychotropic, radiopharmaceutical or consist of or contain a genetically modified organism or organisms.

Please note that it is not possible to provide one number for maximum total doses of AxMPs in CTIS application form. Please refer to Appendix B AxMPs of the study protocol. Therefore, values for maximum total doses allowed are populated as 9999 mg/kg in CTIS.

Reference Safety Information

The Reference Safety Information for vedolizumab IMP may be found in the Investigator Brochure section 6.4.1.

The Reference Safety Information for the auxiliary medication can be found in the representative SmPC provided as part of the submission.

In-vitro diagnostic medical devices

Takeda hereby declares that there are no medical devices which are to be investigated in this clinical trial.

Sponsor's Statements

Takeda does not consider this trial to be a low-interventional trial.

Nonclinical Good Laboratory Practice (GLP) safety pharmacology studies and GLP toxicology studies have been conducted and are supportive for the doses, dose regimens, and dosing duration proposed for the Phase 3 study. For a description of the Sponsor's non-clinical experience with Vedolizumab, please refer to the enclosed Investigators Brochure.

Additional Local Requirements

For any additional information according to Member State requirements (CTIS Part II), please refer to the Appendices to the cover letter.

We trust that the above information and the submitted documents are sufficient to support the assessment of this clinical trial application. If you require further information, please do not hesitate to contact us.

Best Regards, Takeda Development Center American Inc.