Clinical Study Protocol

NCT Number: NCT03710486

Title: Vedolizumab and anti-TNFs Outcomes in Real-World Biologic Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) – IBERIA

Study Number: Vedolizumab-5047

Document Version and Date: 2.0, 23 May 2019

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

Non-Interventional Study Protocol

Title: Vedolizumab and anti-TNFs Outcomes in Real-World Biologic Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) – IBERIA

Short title: Vedolizumab and anti-TNFs Outcomes in Real-World Biologic Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) – IBERIA

Spanish Health Authorities Study code: TAK-VEZ-2018-01

Study ID: Vedolizumab-5047

Sponsor: Takeda Farmacéutica España SA
C/ Alsasua 20, 28023 (Madrid)
Phone: + *0034917149900*

Study phase: Medical Affairs, Post-Approval Company Sponsored (Observational)

Protocol final version: 2.0, 23 May 2019

1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	Iberia Contact
Serious adverse event and pregnancy reporting	[redacted]
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	[redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

[redacted]

[redacted]

[redacted]

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

<Investigator Name (print or type)>

<Investigator's Title>

<Location of Facility (City, State/Provence)>

<Location of Facility (Country)>

STUDY SUMMARY

Name of Sponsor(s): Takeda Farmacéutica España SA.	**Compound/Product:** Vedolizumab, Adalimumab, golimumab, infliximab.
Title of Protocol: VEDOLIZUMAB and anti-TNFs Outcomes in Real-World Biologic Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) -IBERIA	
Study Number: Vedolizumab-5047	**Phase:** IV
Study Design: Multicentre, retrospective cohort study of the medical charts of patients who were diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) and who initiated first-line or second-line treatment with vedolizumab (VDZ) or another biologic agent (infliximab, adalimumab, or golimumab [UC only]) (index event) during the eligibility period.	
Primary Objectives: – Describe treatment patterns associated with first-line and second line biologic use (VDZ or other biologic: infliximab, adalimumab, or golimumab, [UC only]) (e.g., dose escalation, treatment discontinuation, and switching). – Describe the real-world clinical effectiveness of the use (first-line and second line) VDZ vs. other biologics at least 6 months post-treatment initiation.	
Secondary Objectives: – Characterize patients treated with VDZ or other biologics (infliximab, adalimumab, or golimumab [UC only]) as first and second line biologic therapy in terms of demographics, medical, and treatment histories. – Describe the real world clinical effectiveness of VDZ vs. other biologics at least 12 months post-treatment initiation (in a subgroup of patients with adequate follow-up available). – Describe the safety events occurring post biologic treatment initiation (VDZ or other biologics). – Quantify healthcare resource utilization including the rates of healthcare professional (HCP) and emergency department (ED) visits, hospitalizations and Inflammatory Bowel Disease (IBD) related surgical procedures.	

[redacted]

Subject Population:

The study population consists of two distinct first line and second-line biologic treatment cohorts of adult patients:

- VDZ Cohort: Patients with UC or CD who have initiated VDZ as a first-or second-line biological treatment.
- Other Biologic Cohort: Patients with UC or CD who have initiated other biologic treatment (infliximab, adalimumab, or golimumab [UC only]) as first-or second-line biological treatment.

Number of Subjects:	**Study Sites:**
The target sample size is 400 patients with a confirmed diagnosis of UC or CD – 200 patients treated with first-line or second-line VDZ – 200 patients treated with a first-line or second-line other biologics (originator or biosimilar products with market authorization)	The participation of 25 centers (20 in Spain and 5 in Portugal) is foreseen.
Dose Level(s): Active substances: Vedolizumab 300mg, Adalimumab 20 mg, Golimumab 50 mg, Infliximab 100 mg. Medical products: ENTYVIO®,Humira®, Simponi®, Remicade®, Remsina®, Flixabi®	**Route of Administration:** Intravenous/subcutaneous.

Duration of Study:

Overall Study Duration: 24 months

Enrolment period: 12 months

Treatment/Follow-up: N/A

Main Criteria for Inclusion:

1. The patient has a diagnosis of moderate to severe UC or CD documented in the medical chart.
2. The patient received at least one dose of VDZ or other biologic (infliximab, adalimumab, or golimumab [UC only]) during the eligibility period.
3. The patient was 18 years of age or older at the time of starting treatment with VDZ or other biologic (index event).
4. The patient received the biologic treatment as first-line or second-line biologic for UC or CD.
5. Patient has a minimum of six months of follow-up between date of starting biologic treatment (index event) and the date of completion of the patient pre-screening registry.

Main Criteria for Exclusion:

1. Patient received VDZ or another biologic as part of an interventional clinical trial ever in their lifetime (includes index treatment).
2. Patient's index treatment was another biologic therapy other than VDZ, infliximab, adalimumab, or golimumab [UC only].
3. Patient initiated index treatment as combination therapy with two biologic agents.
4. The biologic was prescribed for the treatment of perianal disease.
5. The patient has received a biologic prior to the index period for a disease other than inflammatory bowel disease.
6. The patient's clinical record is unavailable.

Main Criteria for Evaluation and Analyses:

The primary outcomes are the description of treatment patterns (changes in dose and regimen, concomitant treatments, discontinuation) and effectiveness (change in disease activity, biomarkers, qualitative outcomes) in patients with CD and UC following initiation of VDZ or other biologic therapy.

Secondary outcomes include the description of demographic characteristics, frequency and type of adverse events, and the resource utilization during treatment with VDZ or other biologic therapies.

Statistical Considerations:

Data analysis will be primarily descriptive. Analysis will be conducted by index treatment cohort (VDZ vs. other biologics) and then further stratified (if sample size allows) by age and disease type (CD or UC). Simple statistical tests will be conducted to test for significant differences between cohorts (e.g., t-tests and chi-square tests).

An interim analysis is planned prior to database lock. The interim analysis is foreseen by October 2019, although timing may depend on the number of patients included (and data abstracted) as well as deadlines for submission to congresses of interest. Final analyses will be performed once the data from all patients has been collected in the database, cleaned, and database has been lock.

A statistical analysis plan (SAP) will be developed that defines all analytic populations and subpopulations, including definition of treatment response and effectiveness. The SAP will further provide a detailed description of analyses to be performed and describe methods to deal with missing data and censoring. The final SAP will include (empty) table shells to be populated during the final data analysis.

Sample Size Justification:

As the primary objective is descriptive, the sample size will be estimated based on the precision of a confidence interval estimation of a proportion. Assuming the scenario of maximum indetermination (i.e., an expected proportion of 50%), to obtain a confidence interval of 95% of this proportion with a precision of 7.5% is necessary to recruit 171 patients. We expect a 10% of non-valid data so we will recruit 200 patients per group (400 patients in total).

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List of Abbreviations and Definition of Terms

ADR	Adverse drug reaction
AE	Adverse event
Anti-TNF	Anti-tumour necrosis factor
Anti-TNFα	Anti-tumour necrosis factor –alpha
BMI	Body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRO	Contract research organization
CRP	C reactive protein
CT	Computerized tomography
DRG	Diagnosis-related group
eCRF	Electronic case report form
ED	Emergency Department
EDC	Electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR	Erythrocyte sedimentation rate

EU	European Union
FCP	Fecal calprotectin
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HBI	Harvey-Bradshaw Index
HCP	Healthcare professional
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
ID	Identification
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MedDRA	Medical Dictionary for Regulatory Activities
PDL	Patient disposition log

PGA	Physician Global Assessment
PI	Principal investigator
PQI	Product Quality Issue
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SES-CD	Simple Endoscopic Index for Crohn's Disease
SOPs	Standard operation procedures
SSRs	Special Situation Reports
TNFα	Tumour necrosis factor –alpha
UC	Ulcerative colitis
UK	United Kingdom
US	United States of America
VDZ	Vedolizumab

2 Introduction

Inflammatory bowel disease (IBD) is a collective term for a number of conditions that manifest through the inflammation of the gastrointestinal tract. The most common forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which can be differentiated by the areas of the gastrointestinal tract that are affected (other important pathological and diagnostic differences also occur).

There is evidence that the worldwide incidence and prevalence of IBD is increasing.[1] There is considerable geographic variation in both the prevalence and incidence of CD and UC across Europe, with the highest rates of IBD reported in Northern Europe, especially Scandinavia and the United Kingdom (UK), while IBD is relatively rare in Eastern Europe.[2] In the United States (US), the prevalence of CD in adults has been estimated to be 201 (95% CI: 197, 204) per 100,000, and of UC to be 238 (95% CI: 234, 241);[3] the US average annual age/gender-standardised incidence is estimated to be 33 (range: 27–40) per 100,000, and 50 (range: 36–55) per 100,000 respectively.[3] An estimated 2.5–3 million people in Europe are affected by IBD, with a direct healthcare cost of 4.6–5.6 bn Euros/year.[2]

IBD is associated with significant patient morbidity and negatively impacts HRQoL.[4] Furthermore, patients with IBD consume substantial health care resources, with increased hospitalizations, ED visits, and clinician office-based visits.[5]

Traditionally, patients with mild or moderate IBD are treated with aminosalicylates as first-line therapy, with progression to second-line/add-on therapy comprising of glucocorticoids or immunomodulators if symptoms persist or intensify. Patients with moderately or severely active disease may be treated with tumour necrosis factor-alpha (TNFα) antagonist therapies such as infliximab, adalimumab, and golimumab. However, due to safety risks associated with systemic immunosuppression and the significant primary non-response and secondary loss of response experienced on these current therapies, novel treatments are warranted. Patients with a diagnosis of UC who do not respond to treatment, have waning response to treatment, or whose symptoms intensify, may also undergo surgery. Maintenance therapy following remission of symptoms varies but typically includes the use of biologics (e.g., anti-TNFα).[6,7]

However, due to the significant failure rate and side effects associated with current IBD therapies, novel therapies for the treatment of IBD are warranted. New biologic agents are being investigated for use in patients with IBD.[8]

Vedolizumab (VDZ; originator product name: ENTYVIO®) is the first gut-selective monoclonal antibody developed by Takeda for the treatment of both UC and CD that targets α4β7 integrin, blocking lymphocyte trafficking to the gut, which differentiates its mechanism of action compared to the other biologic therapies listed above. In the double-blind randomised GEMINI clinical trials, VDZ was shown to maintain clinical remission and improve HRQoL at 52 weeks and 152 weeks post-treatment initiation in patients with moderately-to-severely active UC.[9–11]VDZ was licensed for the treatment of CD and UC by the US Food and Drugs Agency.[7]and by the European Medicines Agency.[12] VDZ was launched in Spain and Portugal on 30 June 2014 and January of 2017 respectively for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or are intolerant to conventional treatment or with an antagonist of tumor necrosis factor alpha (TNFα); for CD, VDZ is approved for use in adult patients who have had an inadequate response, loss of response, or are intolerant to conventional treatment or with an antagonist of tumor necrosis factor alpha (TNFα) (ENTYVIO® EMA Technical Data Sheet or Summary of Product Characteristics).[13] VDZ can be used in patients who are naïve to prior biologics as well as patients who received one or more prior biologic regimens.[12] In the real-world, there are only a few reports on the comparative effectiveness of VDZ to other biologics in UC and CD patients, especially in those naïve to prior biologic therapy. The majority of real-world data generated to date on VDZ has primarily focused on anti-TNF refractory cohorts;[14,15] hence, there is a need to generate additional evidence on outcomes in bio-naïve cohorts, where preliminary observations may suggest improved outcomes relative to patients on anti-TNF therapies.[2] These data will be important to understand positioning of VDZ in the treatment pathway as well as supporting the development of treatment guidelines and informing clinical-decision making.

The efficacy and safety of VDZ for the treatment of UC and CD was demonstrated in the GEMINI clinical trial programmes,[9–11,14,16] which included both biologic-naïve patients and

patients who had failed prior anti-TNFα treatment. In the real-world, there are only a few reports on the comparative effectiveness of VDZ to other biologics in UC and CD patients, especially in those naïve to prior biologic therapy. The majority of real-world data generated on VDZ to date has primarily focused on anti-TNF refractory cohorts[17–19]; hence, there is a need to generate additional evidence on outcomes in bio-naïve cohorts, where preliminary observations may suggest improved outcomes relative to anti-TNFα experienced patients.

3 Study Objective(s) and Outcome(s)

3.1 Objective(s)

The overall purpose of the study is to evaluate treatment effectiveness, treatment patterns, health care resource utilization, and safety of VDZ in patients with UC and CD as first line (patients who were biologic-naïve at the start of therapy) or second-line biologic therapy (patients who discontinued treatment with first TFNα inhibitor). A cohort of patients with UC or CD who were prescribed an anti-TNFα will also be included in this study to facilitate the descriptive analysis of treatment effectiveness in the VDZ cohort. In order to evaluate VDZ and provide a real-world treatment landscape with anti-TNFα therapies in Spain and Portugal, data will be collected retrospectively from the patients' medical charts.

3.1.1 Primary Objective(s)

1. Describe treatment patterns associated with first-line and second line biologic use (VDZ or other biologic: infliximab, adalimumab, or golimumab [UC only]) (e.g., dose escalation, treatment discontinuation, and switching).

2. Describe the real-world clinical effectiveness of the use (first-line and second line) VDZ vs. other biologics at least 6 months post-treatment initiation.

3.1.2 Secondary Objective(s)

1. Characterize patients treated with VDZ or other biologics (infliximab, adalimumab, or golimumab [UC only]) as first and second line biologic therapy in terms of demographics, medical, and treatment histories.

2. Describe the real world clinical effectiveness of VDZ vs. other biologics at least 12 months post-treatment initiation (in a subgroup of patients with adequate follow-up available).

3. Describe the safety events occurring post biologic treatment initiation (VDZ or other biologics).

4. Quantify healthcare resource utilization including the rates of healthcare professional (HCP) and emergency department (ED) visits, hospitalizations and IBD-related surgical procedures.

[redacted]

3.2 Outcome(s)

3.2.1 Primary Outcome

The primary outcomes are the description of treatment patterns (changes in dose and regimen, concomitant treatments, discontinuation) and effectiveness (change in disease activity, biomarkers, qualitative outcomes) in patients with CD and UC following initiation of VDZ or other biologic therapy. Clinical effectiveness will be evaluated at a minimum of 6 months post-treatment initiation and treatment patterns will be evaluated throughout the patients' -post-index event period. For patients who discontinue index VDZ or other biologic therapy, the collection of data pertaining to clinical effectiveness and treatment patterns will end at the earliest of 6 months post-index treatment discontinuation or date of death, loss to follow-up or chart abstraction initiation. A brief description of these analyses is provided in section 9.1; a detailed description of the analyses will be included in the SAP.

3.2.2 Secondary Outcome(s)

Secondary outcomes include the description of demographic characteristics, frequency and type of adverse events, and the resource utilization during treatment with VDZ or other biologic therapies (post-index event period). For patients who discontinue index VDZ or other biologic

therapy, the collection of data pertaining to response, and safety events will end at the earliest of 6 months post- index treatment discontinuation or date of death, loss to follow-up or chart abstraction initiation. All analyses will be stratified by previously defined subgroups where data are available. A brief description of these analyses is provided in section 9.1; additional details will be described in the SAP.

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in 25 hospitals (20 sites in Spain and 5 in Portugal) treating patients with UC and CD with VDZ and other biologics (infliximab, adalimumab,or golimumab [UC only]).

The Sponsor will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

4.2 Sponsor personnel

The Sponsor will keep a record of all relevant sponsor personnel. This record should include Coordinating Study Managers, local Study Managers and other medical staff, medical responsible for the study, drug safety responsible for the study.

4.2.1 Sponsor responsible persons

4.3 Contract Research Organisation (CRO)

The CRO will keep a record of all involved CRO personnel.

4.3.1 CRO responsible persons

5 Ethics

Owing to the retrospective design, this study does not result in interference with standard medical care and, therefore, it will not affect treatment of study participants. The study will be managed by Bioclever 2005 S.L (Spain) and EUROTRIALS-Consultores Científicos, S.A. (Portugal), hereinafter referred to as Contract Research Organizations (CRO). The study is sponsored by Takeda Farmacéutica España SA., hereinafter referred to as the Sponsor. No patient-identifying information will be transferred to the Sponsor or to the CRO. All data collected will be managed in accordance to local and European laws for personal data protection in force at the moment of protocol approval by the competent independent ethics committee (IEC)/international review board (IRB).

5.1 Ethical conduct of the Study

The study will be conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) (as applied to observational research), all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2013,[20] including, but not limited to:

- Central IRB and local IEC review and approval of study protocol and any subsequent amendments
- Investigator reporting requirements.

The study will be conducted in accordance with legal and regulatory requirements in force in Spain and Portugal, as well as with scientific purpose, value and rigor and will follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP)[21] issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical

Sciences (CIOMS), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (February 2011). Data will be managed in accordance to the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union.[22]

The Sponsor and/or the appointed CRO will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

The sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

5.2 Independent Ethics Committee / Institutional Review Board and Authorities IEC/ IRB

Before study initiation, the protocol will be submitted for review and approval to the appropriate IEC/IRB or equivalent group charged with this responsibility in Spain and Portugal, respectively. The CRO will provide assistance in IEC/IRB submission. When local approval is obtained, the CRO will send the documentation indicating the IEC/IRB (if applicable) Committee's approval or favorable opinion to the study Sponsor before the recruitment process begins.

According to applicable regulations, the appointed CRO or the Site Study Responsible will notify or obtain approval from the relevant IEC/IRB of the protocol, as well as any amendments, and will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results

The Sponsor or the appointed CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Site Responsible with a copy of this list. Copies of the documentswill be distributed upon request.

5.3 Authorities

The Sponsor or the appointed CRO will send required documents to the competent authority and/or other national or regional authorities. The Sponsor or the appointed will keep an updated list of submission and approval dates and a copy of all documents submitted.

5.4 Subject Information and Written Informed Consent

The Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (and if applicable, the parent or legal guardian) can understand, and obtain the subject's (and if applicable, the subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, parent or legal guardian) must be left with ample time to consider and to pose questions. Since the study is retrospective, the consent only concerns the data collection per se and it does not consent to any interventional procedure or treatment.

The subject must agree that sponsor personnel, their representatives or IEC/IRB or competent authority personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject and parent or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.

For details, see the Subject Information Sheet and Informed Consent Form.

5.4.1 Informed Consent Procedures

Data chart abstraction will not begin until the patient has signed the informed consent in which he/she accepts to participate in the study.

In sites in Spain, in case of deceased patients, the signature of the informed consent will not be necessary. Nevertheless, for these cases, the IEC/IRB involved in the study approval will be informed of the signature exemption of the informed consent, and the use of the data of these patients for the study will be documented in the medical chart by the principal investigator.

In Portuguese sites, in the case of deceased patients, informed consent will be requested from a family member, legal representative or heir, and the use of the data of these patients for the study will be documented in the medical chart. The person obtaining consent is responsible for ensuring that each participant fully understands the nature, purpose, procedures, risks, and benefits of the study. Each participating patient will be provided with a copy of his/her signed informed consent form.

5.5 Participant Confidentiality

All data collected in this study will be strictly confidential in accordance with Spanish and Portuguese regulations, as well as the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union.[22] Personnel from the following organizations may examine the research study records: CRO and regulatory agencies. To safeguard patient confidentiality, the eCRF in the EDC system will record subjects only by means of an anonymous, unique identification code assigned by the EDC system. No information such as initials, date of birth, or local case study identification number that could subsequently be used to identify patients will be entered into the EDC system. Only Principal Investigators, or site personnel delegated by him/her, will have the possibility of associating the de-identified assigned identification code to a specific subject.

It is the participating site's responsibility that sufficient information related to the identity of the patients will be retained. Site study staff will be instructed to maintain complete

confidentiality of all collected data. The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. By signing the protocol, the Institution and/or PI commit to complying with all related applicable local laws and regulations as well as any applicable Spanish and Portuguese regulations, as well as the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union.

The summary report generated from the eCRF will not contain any participant identifying information.

6 Study Design and Plan

This study is a 'non-interventional study' as defined in Directive 2001/20/EC,[23] and will follow the guidelines for GPP.

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.

The study is an ethics-approved, designed as a multicentre, retrospective cohort study of the medical charts of patients who were diagnosed with CD or UC and who initiated first- or second-line biologic treatment with VDZ or another biologic (infliximab, adalimumab, or golimumab [UC only]) (index event) during the eligibility period: January 2017 to date of site initiation.

The target sample size is approximately 400 patients[a] (200 patients per treatment cohort: 1) VDZ and 2) other biologics. It is estimated that these patients will be included from across ~25 sites (20 in Spain and 5 in Portugal), resulting on average in ~8 patients per treatment cohort/site[b]. The medical charts of patients with UC or CD who initiated first-line or second-line biologic treatment with VDZ or another biologic (infliximab, adalimumab, or golimumab [UC only]) during the eligibility period will be identified for potential enrolment.

[a] Final sample size may vary depending on number of eligible patients available for inclusion at participating sites.

[b] Based on interest in participation and the number of eligible patients each site can contribute, the total number of sites enrolled as well as patients per site could increase/decrease.

6.1 Study Period

The study eligibility period will be between January 2017 until date of site initiation and is defined as the period of time within which patients with UC or CD who initiated first or second-line treatment with VDZ or other biologic (index event) are identified for enrolment into the chart review study.

Data collection spans two main periods anchored to the date of index event:

- **Pre-Index Event Period**: Begins on the date of diagnosis of UC/CD and ends one day prior to the date of index VDZ or other biologic treatment initiation during the eligibility period.
- **Post-index Event Period**: Begins on the date of index VDZ or other biologic treatment initiation during the eligibility period and ends at the earliest of 6 months -post-index treatment discontinuation, death, loss to follow-up, or date of chart abstraction initiation.

It is estimated that data abstraction will be completed over a 12 month period between February 2019 and February 2020. In order to avoid selection bias, sites may be instructed to start data abstraction selecting a random sample of all eligible patients with at least six months duration between date of index treatment initiation and date of chart abstraction (see section 6.6.3). It is anticipated that, at a minimum, patients will contribute six months of data -post-index treatment initiation and a maximum of approximately 23.5 months.

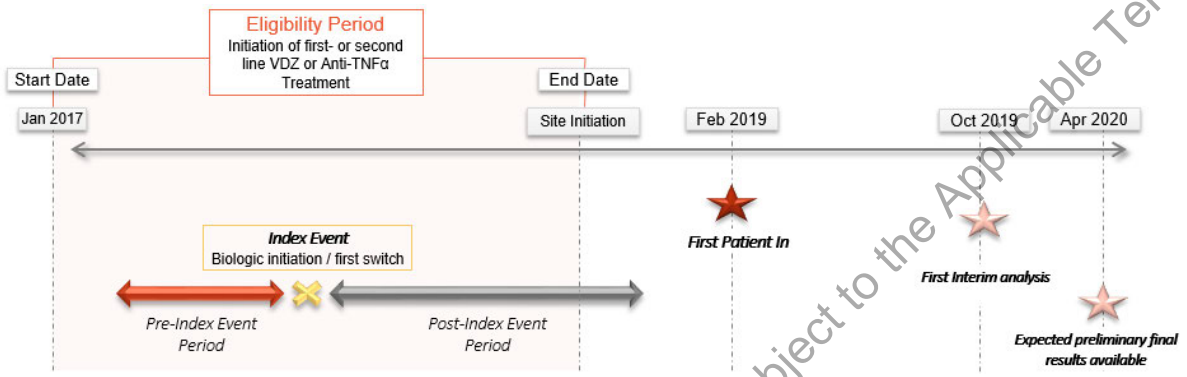
Data collection is estimated to be completed by February 2020. This date is subject to change pending duration of study start-up activities (IEC/IRB approvals) and the date that sites are eventually initiated.

Figure 1 shows an overview of the eligibility and study periods. According to the proposed design:

- All medicinal products were prescribed in accordance with the terms of the marketing authorisation(s)

– The prescription of is clearly separated from the decision to include the subject in the study

Figure 1. Study design overview



6.2 Study Schedule

Planned Start of Study:	February 2019
Planned collection of first data point:	May 2019
Planned End of Study:	February 2020
Planned collection of the last data point:	February 2020
Planned completion of the Statistical Analysis:	April 2020
Planned completion of the Study Report:	June 2020

The Start of Study is defined as the date the first IEC/IRB approves the study protocol. The End of study is defined as last data point collected.

The Sponsor will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB for each site, for each country and for the complete study, as locally required.

The Sponsor will ensure that results are posted on "clinicaltrials.gov" and as required by local authorities.

Based on upcoming knowledge, the Sponsor might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs and authorities will be informed promptly.

6.3 Discussion of Study Design

The study is aimed to gather real-world data of patients treated with first-and second-line biologic therapies for UC and CD. Therefore, the retrospective design is considered most appropriate to capture the actual scenario of routine clinical practice in the management of patients with UC or CD who start biologic therapies.

Although the study objectives are mainly descriptive and do not rely on comparisons, two cohorts have been established based on the type of biologic agent. The rationale for the double cohort is the different mechanism of action of these agents, which is likely to bias the study results in case a single study group is considered.

The number of included sites (25 sites foreseen) is deemed high enough to achieve a reasonable generalizability of the results.

6.3.1 Limitations

This retrospective study design is associated with some methodological limitations.

To start, the quality of the data is dependent on completeness and accuracy of the data documentation available in the medical records. Existing medical chart data may not contain all of the information required to address the study objectives; data availability as a result of differences in HCP usual care documentation may vary across charts. However, it is expected

that data supporting the primary and secondary objectives should be of reasonably good quality across sites. This will be evaluated during the feasibility assessment phase of the study.

It may be possible that sites included in the study may not be fully representative of usual care patterns of UC and CD in Spain and Portugal. Additionally, variation in patient identification procedures by the sites could also lead to selection bias. To address these issues, efforts will be made to include sites in this study that vary by geographical location (different provinces) and institution type to increase generalizability of the data. In addition, the patient identification process at the sites will be documented and monitored by the CRO to reduce this risk of bias. Sample size targets will be set for each site and for sites with sampling frames larger than set targets for VDZ and other biologic cohorts, random sampling will be undertaken by the CRO.

Subgroup analyses by IBD type (UC vs. CD) and treatment lines (first vs second) will depend on the actual distribution of these patients in usual care, which may limit the robustness of the analysis. If a particular cohort is under-represented in the population, best attempts will be made during patient recruitment to enroll these patients. Other sub-group analyses may be identified post-hoc during analysis.

Similarly, due to the chart review study paradigm, applying 1:1 matching techniques to conduct a comparative analysis between VDZ and other biologic patients at time of enrolment is not feasible. Matching will be limited to post-hoc analytic techniques which may require an over-sampling of patients from the other biologic reference cohort. There will also be limitations to the extent of 1:1 matching of characteristics between subjects which may impact the comparativeness of the two cohorts.

In addition to the design-specific limitations, the limited time period since VDZ approval in Portugal (January 2017), may jeopardize patient recruitment in this country, leading to a biased study cohort (i.e., according to the study protocol, patients must have been followed up for at least six months since treatment start). This potential risk will be addressed during the feasibility assessment phase of the study.

6.4 Site selection

Approximately 25 sites, 20 in Spain and 5 in Portugal, that treat patients with UC and CD with VDZ and other biologics (infliximab, adalimumab, or golimumab [UC only]) will be selected for participation in this study. To represent variations in current real-world patterns of care, where possible, sites will be selected on the basis of geographic region (e.g., different provinces), and institution size and type (e.g., academic vs. community).

The clinical sites will be evaluated prior to enrolment into the study through a structured feasibility process. As part of the feasibility process, centres will complete a feasibility questionnaire to evaluate the number of potentially eligible patients, data availability, staff resourcing, etc.

6.5 Selection of Study Population

The study population consists of two distinct first-line and second-line biologic treatment cohorts:

- **VDZ Cohort**: Patients with UC or CD who have initiated VDZ as a first-or second-line biological treatment.
- **Other Biologic Cohort**: Patients with UC or CD who have initiated other biologic treatment (infliximab, adalimumab, or golimumab [UC only]) as first-or second-line biological treatment.

Irrespective of the biological therapy prescribed for UC or CD, patients must meet all selection criteria.

6.5.1 Inclusion Criteria

To be considered eligible, the subject must meet the following inclusion criteria:

1. Patient has a diagnosis of moderate to severe UC or CD documented in the medical chart.
2. Patient received at least one dose of VDZ or other biologic (infliximab, adalimumab, or golimumab [UC only]) during the eligibility period.

3. Patient was 18 years of age or older at the time of treatment initiation with VDZ or other biologic (index event).
4. Patient received the biologic treatment as first-line or second line biologic for UC or CD.
5. Patient has a minimum of six months of follow-up between date of starting biologic therapy (index event) and the date of completion of the patient pre-selection registry.

6.5.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Patient received VDZ or another biologic as part of an interventional clinical trial ever in their lifetime (includes index treatment).
2. Patient's index treatment was another biologic therapy other than VDZ, infliximab, adalimumab, or golimumab [UC only].
3. Patient initiated index treatment as combination therapy with two biologic agents.
4. The biologic was prescribed for treatment of perianal disease.
5. The patient received biologic therapy before the index period for a disease other than inflammatory bowel disease.
6. Patients' medical chart is unavailable.

Patients should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available will not be included in or will be deleted from the database.

6.6 Patient selection

6.6.1 Sampling Frame Identification

All patients 18 years of age or older with UC or CD who initiated first-line or second-line biologic treatment with VDZ or one of 4 other biologics (infliximab, adalimumab, or golimumab [UC only]) during the eligibility period (refer to section 6.1) (index event) and meet all selection criteria (refer to sections 6.5.1 and 6.5.2) will be identified at each of the study sites. The sampling frame will comprise these patients. Site staff will record sampling frame patients directly into a Pre-Screening Log, where each patient will be assigned a sequential pre-

screening identification (ID) number. For each patient, site staff will indicate age at index event, date of index event, index treatment type (VDZ, infliximab, adalimumab, or golimumab [UC only]), disease type (UC or CD) and date of most recent visit prior to chart abstraction initiation. The site staff will also receive a file (patient key) where they will record the pre-screening ID and their local patient ID number. This file will be kept at the site and used as a patient key to link the site patient ID number to the study ID number using the pre-screening ID.

6.6.2 Preliminary Target Cohort Selection

The pre-screening log, in which patients are identified by the pre-screening ID only, will be transferred to the CRO, which will create the target cohort of patients at each site following 4-block randomization procedure in which patients will be stratified according to the type of treatment (i.e., VDZ vs. other biologic) and diagnosis (i.e., UC vs. CD). The target cohort will consist of 16 patients per site, balanced in terms of type of treatment and diagnosis. In the event that at any site the number of patients who are possible candidates for inclusion is less than the four patients planned per cohort, the randomization process will not be conducted in that cohort, although this procedure will be performed for the remaining cohorts.

For the preliminary identification of the cohort of interest, consideration shall be given to whether pre-screened patients have been followed up for least 6 months during the eligibility period of the study. Patients who at the time of pre-screening have not been followed up for this period will not be included as potential candidates and will not be taken into account for randomization.

Each site will be provided with the pre-screening IDs of patients selected for the target cohort, who will be offered to enrol the study. In case the patient accepts, he/she will sign the informed consent and a study ID will be assigned to the patient. The study ID of patients who have enrolled the study shall be recorded in the excel-based patient key, which will link the patient's local ID, the pre-screening ID, and the study ID.

In case a patient reject to participate in the study or a screening failure occurs (e.g., the patient does not meet a given inclusion/exclusion criteria), the CRO will randomly select another

patient in the corresponding site following the same procedure. This procedure will be conducted recursively until the final target cohort is achieved or there are no patients left in the sampling frame of the given site. If a site cannot meet the site target, another site may enroll additional cases to make up for deficit.

6.6.3 Screening for Eligibility

Site staff will review the medical charts for all patients in order to determine the sampling frame. Once the patient has been selected and has signed the informed consent, the site staff will record the fulfilment of each inclusion/exclusion criteria in the eCRF. Screen failures (e.g., patients considered for the sampling frame who do not meet the eligibility criteria) will be also recorded in the eCRF.

The overview of the entire patient selection process is represented in Figure 2.

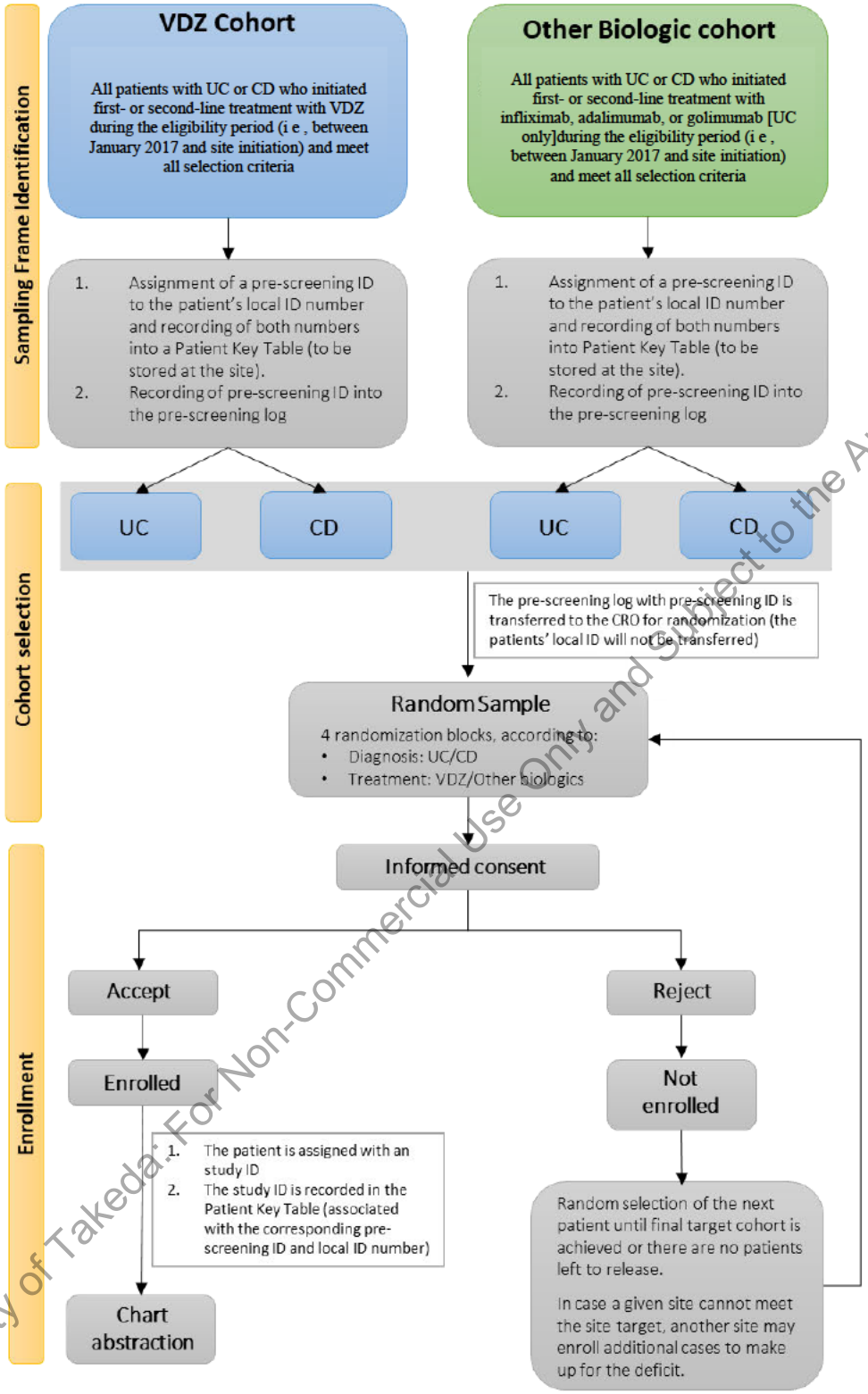


Figure 2. Cohort Identification and Screening for Enrollment

6.7 Treatments

Owing to the retrospective design, treatments no treatments are instructed by the study protocol.

6.8 Premature Termination or Suspension of Study or Investigational Site

6.8.1 Criteria for Premature Termination or Suspension of the Study

As this is a retrospective study, patients have already received treatment at the moment of initiating data collection. Hence, the changes in the use of medications due to safety concerns shall not affect the conduct of the study, which will be completed as planned unless significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives.

6.8.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.8.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an IEC/IRB or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.9 Study Plan

As this is a retrospective study, only remote monitoring visits are foreseen. Once the study sites have been selected based on the feasibility plan (see section 6.4) and the study protocol has been approved by the competent IRB/IEC, investigators in each site will initiate the patient selection process as described in section 6.6).

7 Safety Reporting

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Descriptive statistics will be used to describe all safety events reported during the chart review. Safety data described will include:

- Number and types of AEs associated with medical treatment vs. non-treatment related events
- Number of non-serious and serious AEs documented to be related to treatment
- Number of treatment alterations (withdrawn, reduced, increased) as a result of AEs
- AE duration (based on information on date of onset and date of resolution)
- AE outcome

Safety outcomes will be evaluated from VDZ or other biologic initiation to 6 months -post-index treatment discontinuation. For subjects who are not 6 months post-treatment discontinuation at the time of chart abstraction initiation, the end date will be the date of chart abstraction initiation. All analyses will be finalized in the SAP.

7.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.).

7.1.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

7.1.4 Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Note: All Special Situation (SS) reports and product quality issues will be sent to Takeda, with or without an associated adverse event, as described in section 7.2.

7.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy:
  - Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding:
  - Infant exposure from breast milk.
- Overdose:
  - All information of any accidental or intentional overdose.
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual).
- Suspected transmission of an infectious agent:
  - All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product.
- Occupational exposure.
- Use outside the terms of the marketing authorization, also known as “off-label”.
- Use of falsified medicinal product.

A SSR should be reported even if there is no associated AE (see section 7.2).

7.2 Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance

- **SAEs, AEs, ADRs, SSRs and PQIs in the medical record/source data that are part of the study objectives or outcomes**

  Events/issues which are part of the study objectives or outcomes will be systematically identified and collected from medical records or other applicable source records, and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

- **SAEs, AEs, SSRs and PQIs in the medical records/other applicable source data that are not part of the study objectives and outcomes**

  Events/Issues which are not part of the study objectives and outcomes will not be abstracted or collected from medical records/ source records.

- **SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s).**

  If during the conduct of the study the investigator(s) is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be forwarded to the local Takeda Pharmacovigilance department within 24 hours from reception. This included events spontaneously notified to the investigator(s) which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

  In the event that for the assessment of any adverse reaction, Takeda requires additional information and submit questions to the investigator of the corresponding center, the information answered by the investigator will be considered as follow-up information of the reported adverse events and therefore it will have to be notified to Takeda who requested said information, referring to the adverse reaction initially reported. Such notification to Takeda will be done as described throughout this section.

On a quarterly basis Takeda Pharmacovigilance will send a list of the adverse events received to the CRO in order to perform the corresponding reconciliation process. Then the CRO will send back the discrepancies to Takeda Pharmacovigilance for resolution.

Takeda Contact Information

Spontaneous reports are notified to the local Pharmacovigilance Department in Spain, within 24 hours from reception through the email address **farmacovigilancia@takeda.com** using the Takeda AE reporting form (ANNEX 1).

7.3 Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Authorities

The expedited reporting of AEs and SSRs that are study outcomes to regulatory agencies is not required. Such events should be included in the interim analysis and the Final Study Report.

For spontaneously reported events that are not study outcomes, the Sponsor shall notify regulatory agencies in accordance with local regulatory requirements or Sponsor's post-marketing commitments.

8 Data Quality Control and Assurance

8.1 Quality Control

Systems with procedures will be implemented to ensure the quality of every aspect of the study.

The development of the protocol and SAP will follow internal standard operating procedures (SOPs) of the CRO, which include detailed review rounds. Quality control of the statistical programming will follow the CRO's SOPs.

The EDC system meets approved established standards for the security of health information, is validated and is 21 CFR Part 11/EudraLex Annex 11 compliant. In order to ensure that patient data (as well as other confidential data) remain secure and intact, the CRO follows SOPs and quality control processes that address patient data security. The EDC system has built in edit checks and validations and supports electronically generated and manual queries.

Patient confidentiality will be strictly maintained. Access to the EDC system will be regulated via a hierarchical user-name and password control. Subject data will be de-identified through design of data entry fields that do not permit the entry of identifying information such as initials, date of birth, or centre- assigned patient identifiers. Only trained site staff will enter data into the eCRFs. Patients' ages in whole years, but not date of birth, will be entered. No patient identifiers used by sites will be entered; rather the EDC program will automatically assign a study ID to each patient. The de-identified data as entered into the EDC system will be visible to the CRO and the Sponsor, but only centre staff will be able to trace a study ID number back to a patient identity, a necessary measure to allow centre staff to respond to data queries raised by the CRO later.

8.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

8.3 Inspection by IRB/IEC or Competent Authority

Representatives from IEC/IRB or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Global Research and must make the records available as requested. The Inspector must be reminded up front that consent to access to personal data of deceased patients has not been obtained and that the corresponding IEC/IRB has been informed of the signature exemption of informed consent.

8.4 Data Management

Data Management will be carried out according to a Data Management Plan, which must be written and approved before the design of the study database is finalised. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database. This will not apply to deceased patients with exemption of informed consent signature.

If a subject is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

If a subject is included in the study in spite of being treated off-label (not according to the SPC), data is kept in the database and analysed separately and as part of the overall analyses as described in the Statistical Analysis Plan.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and adverse events/reactions (MedDRA) must be followed.

The study patients will be identified in the database only by Study ID, which may contain information regarding the study site.

8.4.1 Data Collection Tools and Flow

The study site will receive data collection tools (CRFs, access to electronic data capture, etc) from the CRO. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

The study site responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 7 and data on serious AE/ADR reactions collected according to section 7 should be signed off separately by a physician who may or may not be involved in the study.

De-identified data (anonymous to non-site staff) from enrolled patients' medical charts will be abstracted by site staff and entered at the site into the electronic CRFs (eCRFs) of the EDC system.

Over the course of the study, the patient study status (e.g., selected and waiting confirmation of eligibility, enrolled and waiting completion of forms) will be updated automatically within the EDC system. The EDC system will also facilitate the monitoring of the completeness and quality of study data as the study data accrue.

The CRO will provide a web-based EDC system (ENNOV EDC v.8.0.130) to serve as an integrated, transparent tool to collect and manage data and track study progress at the site and patient level.

Screening results for inclusion and exclusion criteria will be captured in the EDC system for all patients in the preliminary target cohort. One eCRF will be completed in the EDC system for each enrolled patient. The completed original eCRFs are the sole property of the study Sponsor and will not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

Each study investigator has ultimate responsibility for the collection and reporting of all data entered on the eCRFs and any other data collection forms (source documents) and ensuring

that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be electronically signed prior to database lock by the study investigator or by an authorized staff member to attest that the data contained on the eCRFs are correctly recorded. The CRO will inform sites when it is time for eCRF sign-off to occur.

In the present case, the source documents are the patients' medical charts and, therefore, data collected on the eCRFs should match the data in the charts.

Site staff will be trained by the CRO to perform the chart abstraction, including data entry and how to retrieve and respond to data queries in the EDC system. It is assumed that all sites will be able to complete data entry into the CRFs via the EDC system.

The EDC system includes logic checks to minimize data entry errors. Data inconsistencies outside the logic checks will be managed by manual queries issued by data management within the EDC system for site completion. All queries will be monitored until resolution within the EDC through the electronic query report.

8.4.2 Data Monitoring

The CRO will provide a web-based EDC system (ENNOV EDC v.8.0.130) to serve as an integrated, transparent tool to collect and manage data and track study progress at the site and patient level.

Quality control mechanisms (e.g., verification of data completeness, validations, and edit checks), which will be automated at time of data entry, will be built into the EDC, and listed in the study Data Management Plan (DMP). Queries will be generated by the CRO for resolution by site staff within the EDC system.

If necessary, a small percent of routine on-site monitoring visits and "For cause" visits (utilised based on pre-agreed triggers) will be performed to ensure appropriate study procedures are being followed and ensure regulatory compliance.

8.4.3 Data Cleaning

In accordance with the DMP, the EDC system will have built-in methods for data validation (e.g., drop down lists, value range controls, and standardised response formats). However, a data cleaning method will furthermore be employed in order to correct inconsistencies or errors that were not captured during data entry (e.g., outliers or conflicting data). Data queries will be identified on an ongoing basis during data collection. Queries will be generated for site completion within the EDC system. Sites will have approximately 5 business days to resolve queries. As database lock approaches, the duration to resolve queries may be less than 5 business days. There will be no formal source data verification (SDV) as data will be de-identified (anonymous to all non-site personnel).

8.4.4 Data Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and medical charts), source documents, detailed records of patient disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator for the length of time specified in local regulations, or in the Site Contract Agreement (whichever time period is longer).

If the investigator becomes unable for any reason (e.g., retirement or relocation) to continue to retain study records for the required period, the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another investigator, another institution, or to an independent third party arranged by the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

8.4.5 Study Variables

Variables including but not limited to the following will be collected, if available. Table 1 summarizes the variable groups and the corresponding timelines in the medical charts.

Table 1. Overview of study variables

	Diagnosis	Pre-index event[1]	Index event	Post-index event[2]
Demographics and medical history			X	
Disease characteristics	X			
Systemic drug therapy history - *Non-biologic drug therapies* - *Biologic drug therapies*		X X		
Laboratory measures			X[3]	X
Disease activity, 'flare-ups' and treatment response/remission		X		X
Comorbid medical conditions and extraintestinal manifestations		X		X
VDZ or other biologic index treatment			X	
Biologic drug therapy switching/ discontinuation				X
Concomitant non-biologic drug therapies			X	X
Adverse events during VDZ and other biologic therapy				X
Healthcare Resource Utilization		X	X	X
Survival status				X

[1]Number in brackets indicates the maximum time period included in the variable assessment.
[2]Up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment.
[3]Most recent measure within 3 months prior to index event.

Demographics and medical history

- Age.
- Sex.
- Weight
- Height
- Smoking status (never, former, current, unknown, including number of years smoked, number of cigarettes smoked per day).

Disease characteristics

- IBD diagnosis characteristics.
    - Date of first-ever diagnosis with IBD (UC or CD diagnosis).
    - Age at first-ever diagnosis (if date is not known).
    - Type of IBD (CD vs. UC).
- UC characteristics at diagnosis
  (Closest assessment to diagnosis, within 3 months post-diagnosis).
    - Location of UC
- CD characteristics at diagnosis
  (Closest assessment to diagnosis, within 3 months post-diagnosis).
    - Location of intestinal involvement
    - Disease behaviour
    - Number and type of active fistulae (if active)

Systemic drug therapy history

- Non-biologic drug therapies (e.g., immune modulators, corticosteroids, antibiotics, 5-ASA): start date, end date, or ongoing at time of index event).
  (Within 6 months prior to the index event)

- Biologic drug therapies
  (Since diagnosis until the index event)

- Therapy type and dosing information (e.g., dose increase or decrease in dosing frequency, date of intensification, discontinuation, date of discontinuation, main reason for discontinuation)

– Laboratory measures

(Most recent measure within 6 months prior to index event and during the post-index event period (including dates of tests and up to 6 months post-index treatment for patients who discontinued their index treatment).

- C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin (FCP), albumin, hemoglobin, and liver profile [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, serum creatinine, blood urea nitrogen (BUN)]).

Disease activity[c], 'flare-ups' and treatment response

– UC disease activity

(Closest assessment within 6 months prior to index event, and all assessments during the post-index event period (including dates of all assessments and up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).

– CD disease activity

(Closest assessment within 6 months prior to index event, and all assessments during the post-index event period (including dates of all assessments and up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).

– UC and CD treatment response.

(Assessments during the post-index event period (including dates of all assessments) up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).

- Complete response (remission), partial response, no response (no remission), response not assessed, or unknown.

[c] Note that the timing of disease activity score assessments and level of documentation in the medical charts is expected to vary.Data availability will be assessed as part of the formal site feasibility assessment.

- Diagnostic evaluations (endoscopic) related to UC or CD during post-index event period.

  (All diagnostic evaluations within 6 months prior to index event, and during the post-index event period (including dates of all assessments) up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).

  - Disease status after diagnostic evaluation (complete remission, partial remission, no remission).

Comorbid medical conditions

- Comorbid medical conditions (includes: chronic conditions, acute events, reactions to prior treatment, and extra intestinal manifestations)

  (Within 6 months prior to index event and pre-existing at time of index event).

  - Type of comorbidity and date of diagnosis.
  - Extra intestinal manifestations change in severity/resolution status post-index event.
- New-onset comorbid conditions (chronic and acute) including extra intestinal manifestations.

  (During the post-index event period up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).

  - Type of comorbidity and date of diagnosis.
  - Extra intestinal manifestations - change in severity/resolution status.

VDZ or other biologic index treatment

- Treatment overview.
  - Type of index treatment (induction and maintenance), type of drug (originator product or biosimilar), date of initiation, steroid dependency status at start of treatment, primary and secondary reasons for selecting treatment.
- Modifications to VDZ/other biologic treatment administration
  - Modification type (e.g., dose increase or decrease in dosing frequency, date of intensification, discontinuation, date of discontinuation, primary reason for discontinuation).

Biologic drug therapy switching

(Only for subjects who discontinued index VDZ/other biologic treatment during the post-index event period: treatment patterns during the post-index event period up to 6 months post-index treatment discontinuation).

- Biologic drug.
  - Type of drug, date of initiation, steroid dependency status at treatment start.
- Treatment overview.
  - Type of index treatment, type of drug (originator product or biosimilar), date of initiation, steroid dependency status at start of treatment, primary and secondary reasons for selecting treatment.
- Modifications to VDZ/other biologic treatment administration
  - Modification type (e.g., dose increase or decrease in dosing frequency, date of intensification, discontinuation, date of discontinuation, primary reason for discontinuation).

Concomitant non-biologic drug therapies

(During the -post-index event period up to 6 months -post-index treatment discontinuation for patients who discontinued their index treatment).

- Type of concomitant non-biologic drug therapy during induction and maintenance, start and end dates, route of administration, administration site.

Adverse events during VDZ and other biologic therapy

(All AEs regardless of seriousness or relation to index therapy that occurred during the post-index event period up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).

  - Type of AE, whether subject also had this AE within 12 months prior to initiation of VDZ or other biologic, severity, AE seriousness criteria assessment, documented relation to index drug noted in chart, date of onset and resolution, action taken with VDZ or other biologic therapy, and outcome.

Healthcare Resource Utilization

- Work status

  At time of the index event

  - Status (e.g., retired, full-time employee)
  - Days of sick leave
- HCP visits/referrals related to UC or CD management.
  - Number of UC/CD-related HCP visits within 12 months prior to index event by HCP type.
  - UC/CD-related HCP visits during the post-index event period up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment.
    - Type of HCP, type of visit, date and reason for visit

- ED visits and hospitalizations for any reason (includes UC/CD related reasons and non-UC/CD related reasons).
  (Within 12 months prior to index event and during the post-index event period up to 6 months post-index treatment discontinuation for patients who discontinued their index treatment).
  - Number of ED and/or Hospitalizations referrals/visits.
- UC/CD-related surgical procedures.
  (During the pre-index event period (from the point of UC/CD diagnosis) and during the post-index event period up to 6 months -post-index treatment discontinuation for patients who discontinued their index treatment).
  - Type of surgical procedure.

Survival status

- Date of death (including primary cause) or last day subject was known to be alive (last contact with site) on date of chart abstraction initiation.

9 Statistical Methods and Determination of Sample Size

This section describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

All final analyses will be performed once the data from all patients has been collected in the database, cleaned, and database lock has occurred.

9.1 Foreseen analyses

This study is observational and epidemiological methods will be employed for data analyses.

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning. The following descriptive analyses are foreseen:

- Continuous data will be described by their mean, median, standard deviation (SD), minimum, and maximum.
- Categorical variables will be described by frequency and percentages (n, %).
- Kaplan-Meier curves will be presented to describe time-to-event analyses (e.g., time to first dose escalation, time to discontinuation).

Treatment patterns will be analysed by index treatment cohort (VDZ vs. other biologic) and then sub-stratified disease type (CD or UC). Simple statistical tests will be conducted (in case data are available) to test for significant differences between cohorts. Appropriate tests (e.g., t-test, Mann Whitney-U test, and chi-square test) will be used for comparison between cohorts.

The following study outcomes have been defined:

9.1.1 Primary outcomes

9.1.1.1 Treatment Patterns

Changes in patients' biologic treatment following initiation of the index treatment will be described across treatment cohorts. Type of treatment will be defined in the SAP. The descriptive analysis will examine:

- Changes in index treatment intensity, such as:
    - Changes in dose (increase or decrease) and frequency of dose intervals (increase or decrease)
- Modifications to planned treatment, such as:
    - Reason for treatment modification related to AEs versus related to disease management
- Concomitant (non-biological) drug treatment
    - Prescribed non-biological drug therapy during post-index period
- Discontinuation of index therapy
- Discontinuation of index therapy with subsequent implementation of another biologic therapy (VDZ, infliximab, adalimumab or golimumab [UC only], tofacitinib, certolizumab and ustekinumab);
    - Switch to either VDZ, infliximab, adalimumab, or golimumab [UC only], tofacitinib, certolizumab and ustekinumab.

Description of specific treatment pattern measures will be further defined in the SAP.

9.1.1.2 Time-to-Event Analysis

Time-to-events (e.g., time-to-switch) will be analysed using survival analysis techniques and Kaplan-Meier curves will be presented. This will allow different follow-up periods for different patients to be accounted for, and for censoring at the end of the observation period (i.e., death and loss to follow-up). The main events evaluated will include:

Time to switching: defined as time from index treatment initiation until a patient initiates another biologic treatment (VDZ, infliximab, adalimumab, or golimumab [UC only], tofacitinib, certolizumab and ustekinumab)

Time to discontinuation: defined as time from index treatment initiation until patient discontinues index treatment without switching to another biologic therapy

Time-to-events analyses will be described across treatment cohorts and by subgroups (i.e., age, disease type, and treatment history) dependent on data availability.

9.1.1.3 Clinical Effectiveness at Least Six Months Post-Treatment Initiation

Clinical effectiveness will be defined by changes in disease measures and outcomes from diagnostic procedures conducted closest to the date of index event, and all assessments during the -post-index event period. All analyses will take into account variations in clinical evaluation time periods to ensure cohorts are comparable. Clinical effectiveness will be described across treatment cohorts and descriptive analysis will examine:

- Changes in disease activity indicators such as changes in scores of the Mayo score, the simple endoscopic index for Crohn's disease (SES-CD), HBI, or CDAI, and/or change to individual components of scores (e.g., change in abdominal pain, change in physician global assessment [PGA], change in abdominal mass, change in stool frequency, or rectal bleeding).
- Changes in clinical assessments such as change in CRP, ESR, FCP.
- Changes based on the evaluation of outcomes associated with diagnostic procedures such as endoscopic findings or other qualitative outcomes provided by HCPs

Definitions of treatment response will be included in the SAP and determined based on the abstracted data variables. Treatment response and clinical effectiveness will be described across treatment cohorts and by subgroups (i.e., IBD type) dependent on data availability.

9.1.2 Secondary outcomes

9.1.2.1 Patient Populations

Patient demographics (e.g., age, smoking status, body mass index, etc.), treatment histories (i.e., prior non-biologic use) and IBD type (UC vs. CD) and disease characteristics (CD/UC) will be summarized.

Sample characteristics will be used to stratify the data into subgroups (i.e., age, diagnosis, treatment, treatment history, treatment lines etc.); subgroup analyses will be conducted throughout as permitted by the availability of data. Variables used in the analysis will be defined further in the SAP.

9.1.2.2 Clinical Effectiveness at Least 12 Months Post-Treatment Initiation

The same analyses conducted at 6 months will be conducted on the sub-set of patients with 12 or more months based on data availability. Treatment response will also be evaluated at 12 months. Definitions of clinical effectiveness and treatment response will be included in the SAP and determined based on the abstracted data variables. Treatment response and clinical effectiveness will be described across treatment cohorts and by subgroups (i.e., IBD type) dependent on data availability.

9.1.2.3 Safety Events

Descriptive statistics will be used to describe all safety events reported during the chart review. Safety data described will include:

- Number and types of AEs associated with medical treatment vs. non-treatment related events
- Number of non-serious and serious AEs documented to be related to treatment
- Number of treatment alterations (withdrawn, reduced, delayed, increased) as a result of AEs
- AE duration (based on information on date of onset and date of resolution)
- AE outcome

Safety outcomes will be evaluated from VDZ or other biologic initiation to 6 months -post-index treatment discontinuation. For subjects who are not 6 months post-treatment discontinuation at the time of chart abstraction initiation, the end date will be the date of chart abstraction initiation. All analyses will be further defined in the SAP.

AEs and SSRs which are study outcomes should be systematically identified and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to the Sponsor.

ADRs reported in the study as well as ADRs reported directly to authorities and to Takeda International Drug Safety according to Section 8 and not captured in the study database will be extracted from the overall safety database and the study database and listed or tabulated in the final report in the standard way of presenting such data in a Periodic Safety Update Report (PSUR).

9.2 Interim Analyses

An interim analysis will be performed sometime prior to database lock. Interim analysis timing will be determined during the data collection period and will be dependent on the number of patients included (and data abstracted) as well as target congress submission deadlines. The analysis is likely to provide an evaluation of data quality as well as provide an understanding of the VDZ study population. Furthermore, the analysis may also examine key study outcomes as well as characterise the populations.

9.3 Determination of Sample Size

The primary objective of the study is descriptive. Therefore, the sample size calculation is based in the precision of a confidence interval estimation of a proportion. The study will recruit two types of patients; the distribution will be 1:1. Both groups will be evaluated separately in consequence we calculated a sample size calculation for each group.

We assumed the scenario of maximum indetermination (i.e., an expected proportion of 50%). To obtain a confidence interval of 95% of this proportion with a precision of 7.5% is necessary to recruit 171 patients. We expect a 10% of non-valid data so we will recruit 200 patients per group (400 patients in total).

- 200 patients treated with a first-line or second-line VDZ.
- 200 patients treated with first-line or second-line of other biologics (infliximab, adalimumab, golimumab).

10 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

11 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor aims to have the results of this study published.

The Sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

Takeda may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

The study team plans to disseminate the results of the study through the development of an abstract, poster/presentation (if selected), final study report, and manuscript.

- **Final Study Report:** A final study report will be developed based on analysis of the final locked dataset. The final study report will include all final study tables.
- **Abstract/Poster:** In the case that results yield material suitable for generation of a conference abstract, an abstract will be prepared. If selected, the study results (either interim or final) will be used to develop a poster/presentation for the conference.
- **Manuscript:** In the case that results yield material suitable for publication of a manuscript in a peer- reviewed journal, a manuscript will be developed. All authors will have to meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship.

An authorship plan will be developed to establish the authorship criteria for publication of the results obtained in this study. To be considered as authors, all investigators should accept and sign the authorship plan.

12 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the below essential documents in the Study Site File:

- Written agreement between the Sponsor or its representative (e.g., CRO) and the Study Site Responsible/Clinic/Hospital/Trust as locally applicable.
- The study protocol and any amendments.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible.
- Subject Information Sheet and Informed Consent Form in local language (notified to / approved by IEC/IRB, including the original signed Forms.
- The list of participating subjects.
- Written IEC / IRB approval / vote according to local regulations.
- Authority approval according to local regulations.
- The completed CRFs.
- The progress reports.

After final database lock the Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 5 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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14 Appendices - List of Stand –alone Documents

1. Takeda AE Reporting Form
2. Study Investigator Agreement
3. Case Report Form
4. Ethics Comitee Approval
5. Summary of Products Characteristics
6. Patient Information Sheet
7. Informed Consent Form
8. Economic Details

ANNEX 1: TAKEDA AE REPORTING FORM

A-IB-SOP-PV-01-C
Version: 03.00

Appendix C: Formulario de notificación de sospechas de reacciones adversas

Takeda

Effective date: 13/08/2018
Version date:05/07/2018
Page 1 of 1

Nº Local Takeda _____

1. Información del paciente

Edad

☐ Hombre ☐ Mujer

Peso kgs

Altura: cms

Origen étnico

¿Ha sido ya notificado a las autoridades? ☐ Si ☐ No

Sólo para uso de Takeda
Fecha de recepción del informe por Takeda:

2. Información del notificador

Nombre del notificador

Dirección del notificador

Código postal

País

Teléfono

Cualificación del notificador:
☐ Médico ☐ Farmacéutico ☐ Otro profesional sanitario * ☐ Abogado
☐ No es profesional sanitario* *Por favor, especificar:

Firma del notificador:

Fecha:

3. Medicamento(s) sospechoso(s): Marca si se conoce	Nº Lote	Indicación	Dosis, unidades y frecuencia	Vía adm.	Fecha inicio	Fecha fin	Acción tomada con el medicamento sospechoso

4. Descripción de la reacción adversa o de la situación especial (sobredosis, abuso, mal uso, fuera de indicación, error de medicación, embarazo, isotanoia, falcificación, etc). (Diagnóstico del efecto adverso(s), y si no se conoce, notificar los síntomas)	Fecha inicio	Fecha fin o duración	Intensidad	** Desenlace
			☐ Leve ☐ Mod. ☐ Severa	
			☐ Leve ☐ Mod. ☐ Severa	
			☐ Leve ☐ Mod. ☐ Severa	

¿Mejoró la reacción adversa al parar o reducir la dosis del tratamiento? ☐ Si ☐ No ☐ n/d
¿Si se reintrodujo el medicamento sospechoso, se repitió el acontecimiento? ☐ Si ☐ No ☐ n/d

** Clave Desenlace: 1 = Recuperado/Resuelto; 2 = Recuperándose/Resolviéndose; 3 = No recuperado/No resuelto; 4 = Recuperado/Resuelto con secuelas; 5 = Mortal; 6 = Desconocido

5. Por favor, notificar información relevante adicional sobre el acontecimiento adverso, algún tratamiento recibido, otras investigaciones.

6. Gravedad: ¿La reacción adversa es grave? ☐ Si ☐ No (En caso afirmativo, por favor, seleccione algún(os) criterio(os))

Muerte ☐ | Amenaza para la vida ☐ | Hospitalización del paciente / Prolongación de la hospitalización ☐ | Resultado de incapacidad o discapacidad persistente o significativa ☐ | Anomalía congénita / Defecto de nacimiento ☐ | Acontecimiento médico importante ☐ | Transmisión de un agente infeccioso a través del medicamento ☐

En caso de muerte, especificar la causa:

Fecha del fallecimiento:

¿Se ha realizado autopsia?
☐ Si ☐ No (En caso afirmativo, por favor, adjunte los resultados)

7. Causalidad: ¿Considera la reacción adversa relacionada con el medicamento sospechoso? ☐ Si ☐ No

8. Historia Médica relevante / Enfermedades concomitantes.
- Por favor, también incluya anteriores reacciones adversas a medicamentos, alergias, factores ambientales, abuso de alcohol y(o) drogas

9. Medicación concomitante (Excluir el tratamiento del acontecimiento)	Indicación	Dosis diaria	Vía adm.	Fecha inicio	Fecha fin

ANNEX 2: STUDY INVESTIGATOR AGREEMENT

ANNEX 3: CASE REPORT FORM

ANNEX 4: ETHICS COMITEE APPROVAL

ANNEX 5: SUMMARY AND PRODUCT CARACTERISTICS OF

ANNEX 6: PATIENT INFORMATION SHEET

ANNEX 7: INFORMED CONSENT FORM

ANNEX 8: ECONOMIC DETAILS