Title
A Retrospective Observational Study to Describe Treatment Patterns, Healthcare Resource Utilisation, Effectiveness and Safety of Vedolizumab (VDZ) and Anti-TNFα in Patients Diagnosed with Crohn’s Disease (CD) or Ulcerative Colitis (UC) in Real-world Clinical Practice in Germany

Protocol Version identifier
2.0

Date of last version of protocol
27 April 2016

EU PAS register number
Study not registered

Active substances
Vedolizumab
Adalimumab
Golimumab
Infliximab

Medicinal products
Entyvio®
Humira®
Simponi®
Remicade®

Product references
EMEA/H/C/002782
EMEA/H/C/000481
EMEA/H/C/000992
EMEA/H/C/000240

Procedure number
Not applicable

Joint PASS
No

Research question and objectives
The primary objectives of the study are to:
- Characterise patients treated with VDZ or an anti-TNFα (infliximab, adalimumab or golimumab [UC only]) treatments in terms of demographics, medical and treatment histories.
- Describe treatment patterns associated with biologic use (VDZ or anti-TNFα: infliximab, adalimumab, or golimumab [UC only]) (e.g., dose escalation, treatment discontinuation, and switching).
- Quantify healthcare resource utilisation including the rates of healthcare professional (HCP) and emergency department (ED) visits, hospitalisations and surgical procedures.

Country of Study
Germany

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Title: Takeda VDZ Chart Review Protocol – Approval

Project #: Vedolizumab-5019/ EVM-18138

Protocol Title: A Retrospective Observational Study to Describe Treatment Patterns, Healthcare Resource Utilisation, Effectiveness and Safety of Vedolizumab (VDZ) and Anti-TNFα in Patients Diagnosed with Crohn’s Disease (CD) or Ulcerative Colitis (UC) in Real-world Clinical Practice in Germany

Protocol number: VDZ 5019
Protocol version and date: Version 2.0, 27 April 2016

Please sign below to indicate that you have reviewed the content of this protocol with the title, number, and version indicated above and that you approve of this protocol.

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature/Date</th>
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<tbody>
<tr>
<td>UBC, Scientific Consultant</td>
<td>/28 Apr 2016</td>
</tr>
<tr>
<td>Evidera, Research Scientist</td>
<td>/04 May 2016</td>
</tr>
<tr>
<td>Evidera, Senior Research Associate</td>
<td></td>
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<tr>
<td>UBC, Associate Project Director</td>
<td></td>
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<tr>
<td>UBC, Project Manager</td>
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<tr>
<td>Takeda, Director, Global Outcomes Research</td>
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## 1. LIST OF ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Term</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Anti-tumour necrosis factor</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>Anti-tumour necrosis factor –alpha</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CDAI</td>
<td>Crohn’s Disease Activity Index</td>
</tr>
<tr>
<td>CEC/LEC</td>
<td>Central ethics committee/local ethics committee</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organisations of Medical Sciences</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CRO</td>
<td>Contract research organization</td>
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<tr>
<td>CRP</td>
<td>C reactive protein</td>
</tr>
<tr>
<td>DRG</td>
<td>Diagnosis-related group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
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<tr>
<td>EDC</td>
<td>Electronic data capture</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ENCePP</td>
<td>European Network of Centres for Pharmacoepidemiology and Pharmacovigilance</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FCP</td>
<td>Faecal calprotectin</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GEP</td>
<td>Good Epidemiological Practice</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
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<tr>
<td>GPP</td>
<td>Good Pharmacoepidemiology Practices</td>
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<td>GVP</td>
<td>Good Pharmacovigilance Practices</td>
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<td>HBI</td>
<td>Harvey-Bradshaw Index</td>
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<td>HCP</td>
<td>Healthcare professional</td>
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<td>HRU</td>
<td>Healthcare resource utilisation</td>
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<td>IBD</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td>ICF</td>
<td>Informed consent form</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>ID</td>
<td>Identification</td>
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<tr>
<td>IEA</td>
<td>International Epidemiological Association</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>InEK</td>
<td>Institute for the Hospital Remuneration System</td>
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<tr>
<td>ISPE</td>
<td>International Society for Pharmacoepidemiology</td>
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<tr>
<td>ISPOR</td>
<td>International Society for Pharmacoeconomics and Outcomes Research</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>PASS</td>
<td>Post-authorization safety study</td>
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<tr>
<td>PDL</td>
<td>Patient disposition log</td>
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<td>PGA</td>
<td>Physician Global Assessment</td>
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<tr>
<td>PI</td>
<td>Principal investigator</td>
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<tr>
<td>PM</td>
<td>Project manager</td>
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<tr>
<td>ROA</td>
<td>Route of administration</td>
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<td>PV</td>
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<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SDV</td>
<td>Source data verification</td>
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<td>SES-CD</td>
<td>Simple Endoscopic Index for Crohn's Disease</td>
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<td>SOPs</td>
<td>Standard operation procedures</td>
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<td>SSR</td>
<td>Special Situation Report</td>
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<tr>
<td>Tx</td>
<td>Treatment</td>
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<tr>
<td>UBC</td>
<td>United BioSource Corporation</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>VDZ</td>
<td>Vedolizumab</td>
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# 2. STUDY CONTACTS

<table>
<thead>
<tr>
<th>Study Contact Name</th>
<th>Address</th>
<th>Telephone/Email</th>
</tr>
</thead>
</table>
| **Sponsor** | Takeda Development Centre Europe Ltd  
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Email: |
| **CRO German Team Lead Clinical Research Associate** | Wallbrunnstr. 24  
Lörrach, Germany 79539 | Tel:  
Email: |
### 3. STUDY SYNOPSIS

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<th>Parameters</th>
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<td><strong>Study Title</strong></td>
<td>A Retrospective Observational Study to Describe Treatment Patterns, Healthcare Resource Utilisation, Effectiveness and Safety of Vedolizumab (VDZ) and Anti-TNFα In Patients Diagnosed with Crohn’s Disease (CD) or Ulcerative Colitis (UC) in Real-world Clinical Practice in Germany</td>
</tr>
<tr>
<td><strong>Background/ Rationale</strong></td>
<td>Since 2001, there have been an increasing number of patients diagnosed and treated with inflammatory bowel disease (IBD) in Germany (Hein et al. 2014). Recent prevalence estimates in Germany report 322 cases of CD (95% confidence interval [CI]: 302,346) per 100,000 and 412 (95% CI: 389,436) cases of UC per 100,000 people (Hein et al. 2014). This is important to healthcare providers as patients with UC and CD consume substantial healthcare resources, with increased hospitalisations, emergency department (ED) visits, and clinician office-based visits in comparison to other patients (Kappelman et al. 2011). Currently, patients with moderately-or-severely active IBD may be treated with anti-tumour necrosis factor–alpha (anti-TNFα) therapies such as infliximab, adalimumab, or golimumab [UC only]. However, due to safety risks associated with systemic immunosuppression and the significant failure rate of these current therapies, novel treatments are warranted. VDZ (Entyvio®), a humanised monoclonal antibody developed by Takeda, is the first integrin receptor antagonist approved that selectively antagonises α4β7 gastrointestinal integrin receptors. VDZ was recently launched in Germany on 15 July 2014 for the treatment of patients with moderate-to-severe active UC and CD. To date, the efficacy and safety of VDZ for the treatment of UC and CD has been demonstrated in both biologic naïve patients and patients with one prior anti-TNFα treatment in clinical trials. However, there are only few reports on the real-world effectiveness of VDZ, particularly in a biologic naïve patient population. Real-world data will help to address this data gap as well as provide a better understanding of the characteristics of patients who are being treated with VDZ, as well as treatment patterns and effectiveness, resource utilisation, and safety-related outcomes. A cohort of patients with UC or CD who were prescribed an anti-TNFα will be included in this study to facilitate the descriptive analysis of treatment effectiveness in the VDZ cohort.</td>
</tr>
<tr>
<td><strong>Study Objective</strong></td>
<td>Primary objectives:</td>
</tr>
<tr>
<td></td>
<td>- Characterise patients treated with VDZ or an anti-TNFα (infliximab, adalimumab, or golimumab [UC only]) treatments in terms of demographics, medical, and treatment histories.</td>
</tr>
<tr>
<td></td>
<td>- Describe treatment patterns associated with biologic use (VDZ or anti-TNFα: infliximab, adalimumab, or golimumab [UC only]) (e.g., dose escalation, treatment discontinuation, and switching).</td>
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<td></td>
<td>- Quantify healthcare resource utilisation including the rates of healthcare professional (HCP) and emergency department (ED) visits, hospitalisations and surgical procedures.</td>
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<td></td>
<td>Secondary objectives:</td>
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<tr>
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<td>- Describe real-world clinical effectiveness at six months post-treatment initiation by index treatment type (VDZ or anti-TNFα) and treatment history (biologic treatment naïve or one prior anti-TNFα treatment).</td>
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<td>- Describe the incidence of real-world adverse events (AEs) occurring during treatment by index treatment type (VDZ or anti-TNFα) and treatment history (biologic treatment naïve or one prior anti-TNFα treatment).</td>
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<td>- Characterise productivity loss (as measured by work loss due to</td>
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### Parameters

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<tr>
<td>Exploratory objective:</td>
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<tr>
<td>• Describe real-world clinical effectiveness at 12 months post-treatment</td>
</tr>
<tr>
<td>initiation (for a subgroup of patients with adequate follow-up time) by</td>
</tr>
<tr>
<td>index treatment type (VDZ or anti-TNFα) and treatment history (biologic</td>
</tr>
<tr>
<td>treatment naïve or one prior anti-TNFα treatment).</td>
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</table>

This is an ethics-approved, single-country, multicentre non-mandated Post-Approval Safety Study (PASS) of patients diagnosed with CD or UC who initiated treatment with VDZ or an anti-TNFα therapy (adalimumab, golimumab [UC only], or infliximab) (index event) during the eligibility period (15 July 2014 to 20 October 2015). Only patients who initiated VDZ or an anti-TNFα and were biologic treatment naïve or received only one prior anti-TNFα treatment regimen will be included in the study.

Assuming a data abstraction initiation date of 20 April 2016 and a study eligibility period starting 15 July 2014 and ending 20 October 2015, the design permits a minimum study follow-up period of six months and maximum of 21 months post-treatment initiation (Index event).

Overall target sample size is approximately 500 charts (250 per treatment cohort: 1- VDZ and 2- anti-TNFα) from approximately 19 sites, which is around 20–30 charts per site. Charts of patients with UC or CD who initiated treatment with VDZ or an anti-TNFα (adalimumab, golimumab [UC only], or infliximab) during the eligibility period will be identified for potential enrolment.

Data collection spans two main periods of time 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 anti-TNFα treatment initiation during the eligibility period.
- **Post-Index Event Period:** Begins on the date of index VDZ or anti-TNFα treatment initiation during the eligibility period and ends at the earliest of death, lost to follow-up or date of chart abstraction initiation.

This study does not result in interference with standard medical care, thus, will not impact the treatment of study participants. The study is sponsored by Takeda Development Centre Europe Ltd., hereinafter referred to as the Sponsor. The study will be managed by Evidera-United BioSource Corporation (UBC), hereinafter referred to as the Contract Research Organisation (CRO). No patient-identifying information will be transferred to the Sponsor nor the CRO.

Data abstraction is forecasted to be completed by August 2016. This date is subject to change pending actual date of chart abstraction initiation.

The study population consists of two distinct treatment cohorts:

1. Patients with UC or CD who initiated VDZ (biologic naïve or had one prior anti-TNFα treatment).
2. Patients with UC or CD who initiated anti-TNFα treatment (biologic naïve or had one prior anti-TNFα treatment).

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1 This date is subject to change pending the actual date that chart abstraction initiates.
2 Total sample size for this study will be dependent on volume of potentially eligible patients available for chart abstraction at participating sites.
3 Depending on interest in participating in this study and volume of potentially eligible patients each site can contribute to this study, total number of sites enrolled into the study could increase/decrease.
4 Site sample size is an approximation since some sites may abstract more or less charts.
### Parameters | Description
--- | ---

**Inclusion Criteria**

Patients must meet all of the following inclusion criteria in order to be enrolled into the study:

1. Patient has a diagnosis of UC or CD documented in the medical chart.
2. Patient received at least one dose of VDZ (Entyvio) or an anti-TNFα (infliximab, adalimumab, or golimumab [UC only]) during the eligibility period (15 July 2014 to 20 October 2015).*
3. Patient was 18 years of age or older at the time of treatment initiation with VDZ or anti-TNFα (index event).
4. Patient was biologic naïve OR had only one prior anti-TNFα treatment at time of index event.

*Note:

- Patients who initiated VDZ and switched to an anti-TNFα during the eligibility period will comprise the VDZ cohort only and will not be included in the anti-TNFα cohort.
- Patients who initiated an anti-TNFα and switched to VDZ during the eligibility period will comprise the VDZ cohort only and will not be included in the anti-TNFα cohort.
- Patients in the anti-TNFα cohort who initiated more than one eligible anti-TNFα during the eligibility period will have only their first eligible anti-TNFα regimen selected as the index event and included in the study.

**Exclusion Criteria**

Patients who meet any of the following criteria will be excluded from the study:

1. Patient received VDZ OR anti-TNFα as part of an interventional clinical trial ever in their lifetime (includes index treatment).
2. Patient's index treatment was an anti-TNFα therapy other than infliximab, adalimumab, or golimumab [UC only] (only applicable to the anti-TNFα cohort).
3. Patient had more than one anti-TNFα treatment prior to index event.
4. Patient initiated index treatment as combination therapy with two biologic agents.
5. Patient received previous treatment with biologic agents for conditions other than IBD ever in their lifetime.
6. Patient’s medical chart is empty or missing.

**Site Selection**

Approximately 19 centres that treat patients with UC and CD with VDZ and anti-TNFαs will be targeted for enrolment in this study. Sites will be administered a structured feasibility questionnaire as part of the site qualification process. To represent variations in current real-world patterns of care, where possible, sites will be selected on the basis of geographic region, institution size, and type (e.g., public vs. private).

**Study Size**

The target sample size is 500 patients with a confirmed diagnosis of UC or CD.

- 250 patients treated with VDZ
- 250 patients treated with an anti-TNFα (originator or biosimilar products with market authorisation)
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
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<tbody>
<tr>
<td>Variables</td>
<td>Categories of variables to be abstracted if available include but are not limited to:</td>
</tr>
<tr>
<td></td>
<td>• Demographics and medical history</td>
</tr>
<tr>
<td></td>
<td>• Systemic non-biologic drug therapy history within two years prior to index event</td>
</tr>
<tr>
<td></td>
<td>• Prior anti-TNFα regimen (for subjects not biologic treatment naïve at index date)</td>
</tr>
<tr>
<td></td>
<td>• Disease characteristics at diagnosis and most recent prior to index event</td>
</tr>
<tr>
<td></td>
<td>• Laboratory assessments within one month prior to the index event and during the post-index study period</td>
</tr>
<tr>
<td></td>
<td>• Disease activity closest to date of IBD diagnosis, closest to the date of index event, and all assessments during the post-index event period</td>
</tr>
<tr>
<td></td>
<td>• Treatment response during post-index period</td>
</tr>
<tr>
<td></td>
<td>• Diagnostic evaluations related to UC or CD closest to date of IBD diagnosis, closest to the date of index event, and all assessments during the post-index event period</td>
</tr>
<tr>
<td></td>
<td>• Comorbid medical conditions (includes: chronic conditions, acute events, reactions to prior treatment and extra intestinal manifestations) within 12 months prior to index event and pre-existing at time of index event</td>
</tr>
<tr>
<td></td>
<td>• New-onset comorbid conditions (chronic and acute) during the post-index event period</td>
</tr>
<tr>
<td></td>
<td>• VDZ or anti-TNFα index treatment (includes: treatment plan and modifications/discontinuation)</td>
</tr>
<tr>
<td></td>
<td>• Biologic therapy switching (only for subjects who discontinued index VDZ/anti-TNFα treatment)</td>
</tr>
<tr>
<td></td>
<td>• Concomitant non-biologic drug therapies during the post-index event period</td>
</tr>
<tr>
<td></td>
<td>• AEs from initiation of index VDZ and anti-TNFα therapy (index event) up to 18 weeks post-treatment discontinuation or date of chart abstraction initiation (whichever comes first)</td>
</tr>
<tr>
<td></td>
<td>• Work status at time of index event and changes to work status during the post-index event period</td>
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<tr>
<td></td>
<td>• Healthcare resource utilisation (HRU)</td>
</tr>
<tr>
<td></td>
<td>o Healthcare professional (HCP) visits related to UC/CD management during the post-index event period</td>
</tr>
<tr>
<td></td>
<td>o Emergency department (ED) visits and hospitalisations within one year prior to index event and during the post-index event period</td>
</tr>
<tr>
<td></td>
<td>o Surgical procedures during the pre-index event and the post-index event periods</td>
</tr>
<tr>
<td></td>
<td>• Survival status on date of chart abstraction initiation</td>
</tr>
</tbody>
</table>

| Data Source and Collection | The source for all data collected will be the patients’ medical charts. Retrospective data will be abstracted from the medical charts of patients and entered into an electronic data capture (EDC) system by trained local site staff. |
Retrospective Chart Review Study in Patients with UC and CD (VDZ 5019)  

27 April 2016

Parameters | Description
--- | ---
**Data Analysis** | Data analysis will be descriptive. Analysis will be conducted by index treatment cohort (VDZ vs. anti-TNFα) and then further stratiﬁed (if sample size allows) by age, disease type (CD or UC), and treatment history (biologic treatment naïve or one prior anti-TNFα treatment). Simple statistical tests will be conducted to test for signiﬁcant differences between cohorts (e.g., t-tests and chi-square tests).

An interim analysis will be performed shortly after the ﬁrst month of data collection has been completed. Final analyses will be performed once the data from all patients has been collected in the database, cleaned, and database lock has occurred.

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.

**Safety Reporting** | Considering the nature of chart review studies, where the AEs occurred sometime in the past and should have been reported at the time of occurrence as per standard practice, this study will summarise the AEs collected to address study outcomes in the ﬁnal study report. Information pertaining to AEs related to VDZ (also known as adverse drug reactions [ADRs]) that do not address study outcomes, spontaneously reported to the CRO and/or Sponsor outside of the EDC system (should this occur), will be transferred to Sponsor German Pharmacovigilance Team for entry into the Sponsor Safety Database within one business day of awareness. The Sponsor will notify regulatory agencies of ADRs in accordance with local regulatory requirements in Germany.

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 in the context of the feasibility assessment that will be undertaken.

**Limitations** | Subgroup analysis at time of VDZ and anti-TNFα initiation by treatment history (biologic naïve vs. one prior anti-TNFα treatment) and disease type (UC vs. CD) may be limited depending on the actual distribution of these patients in usual care.

Applying 1:1 matching techniques at the time of patient enrolment between the VDZ and anti-TNFα cohorts is not feasible in a chart review study paradigm. Matching will be limited to post-hoc analytic techniques.
4. PROTOCOL ADHERENCE AND MODIFICATIONS

The study will be conducted in accordance with the current protocol or protocol amendments. All changes made to the protocol will be tracked in the table below. All protocol and protocol amendments will be agreed upon by the Sponsor and the principal investigator (PI) (Annex 2).

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>26 February 2016</td>
<td>Original</td>
</tr>
<tr>
<td>2.0</td>
<td>27 April 2016</td>
<td>Change to safety reporting process in safety reporting section of study synopsis and section 10 of the protocol. Expedited reporting of AEs documented as related to VDZ is not required and data only need to be summarized in the final report.</td>
</tr>
</tbody>
</table>

5. STUDY MILESTONES*

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Planned Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of Data Collection</td>
<td>April 2016</td>
</tr>
<tr>
<td>End of Data Collection</td>
<td>August 2016</td>
</tr>
<tr>
<td>Final Report of Study Results</td>
<td>December 2016</td>
</tr>
</tbody>
</table>

* All milestone dates are subject to change pending on timing of study start-up and duration of study activities.

6. BACKGROUND

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

There is evidence that the worldwide incidence and prevalence of IBD is increasing (Molodecky et al. 2012). In a recent analysis of an insurance-based cohort in Germany, the prevalence of CD was estimated to be 322 (95% confidence interval [CI]: 302,346) per 100,000, and of UC was estimated to be 412 (95% CI: 389,436) per 100,000. Further analysis of this cohort found a statistically significant trend in increasing prevalence of actively treated IBD between 2001 and 2010 (Hein et al. 2014). There is also 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 (Burisch et al. 2013). 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) (Kappelman et al. 2007); 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 (Hou et al. 2013). Overall, patients with IBD consume substantial healthcare resources, with increased hospitalisations, emergency department (ED) visits
and clinician office-based visits in comparison to other patients, which is important for healthcare providers to better understand (Kappelman et al. 2011).

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. For 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) (Kornbluth et al. 2010; NICE 2013; NICE 2012; Sandborn 2014). However, due to the significant failure rate and side effects associated with current IBD therapies, novel therapies for the treatment of IBD are warranted.

Vedolizumab (VDZ; originator product name: Entyvio®) is a monoclonal antibody developed by Takeda for the treatment of both UC and CD that binds to integrin and has a different target compared to the other biologic therapies listed above. In the double-blind randomised GEMINI clinical trials, VDZ was shown to maintain clinical remission at 52 weeks post-initiation of treatment in patients with moderately-to-severely active CD (Sandborn et al. 2013) and UC (Feagan et al. 2013). VDZ was licensed for the treatment of CD and UC by the US Food and Drugs Agency (FDA 2013) and by the European Medicines Agency (EMA 2014), including Germany, in May 2014. Within the European Union (EU), VDZ is indicated for use in adult patients with moderately-to-severely active UC or CD who have had an inadequate response with, lost response to, or were intolerant to either conventional or anti-TNFα therapy.

6.1. Study Rationale

The efficacy and safety of VDZ in the treatment of IBD has been demonstrated in clinical trials, but its effectiveness in a real-world context is less well understood. Real-world data will also provide a better understanding of the characteristics of patients who are being treated with VDZ, as well as comorbidities, co-medications, and outcomes. Real-world data on the effectiveness and safety of VDZ in key patient subgroups of interest, such as patients who are biologic naïve or received one prior anti-TNFα treatment, may help further the understanding of when to use VDZ in the current treatment landscape.

The purpose of the proposed study is to evaluate treatment patterns, healthcare resource utilisation, effectiveness, and safety of VDZ in patients with UC and CD who were biologic naïve or received one prior anti-TNFα treatment. A cohort of patients with UC or CD who were prescribed an anti-TNFα will 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 Germany, data will be collected from real-world medical charts.

7. STUDY OBJECTIVES

7.1. Primary Objectives

1. Characterise patients treated with VDZ or anti-TNFα (infliximab, adalimumab or golimumab [UC only]) treatments in terms of demographics, medical, and treatment histories.
2. Describe treatment patterns associated with biologic use (VDZ and anti-TNFα infliximab, adalimumab, or golimumab [UC only]) (e.g., dose escalation, treatment discontinuation, and switching).

3. Quantify healthcare resource utilisation including the rates of healthcare professional (HCP) and emergency department (ED) visits, hospitalisations and surgical procedures.

7.2. Secondary Objectives

1. Describe real-world clinical effectiveness at six months post-treatment initiation by index treatment type (VDZ or anti-TNFα) and treatment history (biologic treatment naïve or one prior anti-TNFα treatment).

2. Describe the incidence of real-world adverse events occurring during treatment by index treatment type (VDZ or anti-TNFα) and treatment history (biologic treatment naïve or one prior anti-TNFα treatment).

3. Characterise productivity loss (as measured by work loss due to hospitalisation).

7.3. Exploratory Objective

1. To describe real-world clinical effectiveness at 12 months post-treatment initiation (for the subgroup of patients with adequate follow-up time) by index treatment type (VDZ or anti-TNFα) and treatment history (biologic treatment naïve or one prior anti-TNFα treatment).

8. STUDY METHODS

8.1. Study Design

This is an ethics-approved, single-country, multicentre non-mandated post-authorization safety study (PASS) conducted using a retrospective medical chart review study design of patients diagnosed with CD or UC who have initiated treatment with VDZ or an anti-TNFα therapy (index event) during the eligibility period (15 July 2014 to 20 October 2015) in Germany. Only patients who initiated VDZ or an anti-TNFα and were biologic treatment naïve or who received one prior anti-TNFα treatment regimen will be included in the study.

Overall target sample size is approximately 500 charts (250 per treatment cohort: 1- VDZ and 2- anti-TNFα) from approximately 19 sites, which is approximately 20–30 charts per site. Charts of patients with UC or CD who initiated treatment with VDZ or an anti-TNFα (adalimumab, golimumab [UC only]) and infliximab) during the eligibility period will be identified for potential enrolment.

This study does not result in interference with standard medical care, thus, will not impact the treatment of study participants. The study will be managed by Evidera-United BioSource Corporation (UBC), hereinafter referred to as the Contract Research Organisation (CRO). The study is sponsored by Takeda Development Centre Europe Ltd, hereinafter referred to as the Sponsor. No patient-identifying information will be transferred to the Sponsor nor the CRO.

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5 Total sample size for this study will be dependent on volume of potentially eligible patients available for chart abstraction at participating sites.

6 Site sample size is an approximation since some sites may abstract more or less charts to meet cohort target sample sizes.

7 Depending on interest in participating in this study and volume of potentially eligible patients each site can contribute to this study, total number of sites enrolled into the study could increase/decrease.
8.1.1. Eligibility Period

The study eligibility period is defined as the period of time within which patients with UC or CD who are biologic naïve or had one prior anti-TNFα initiated treatment with VDZ or anti-TNFα treatment (index event) are identified for enrolment into the chart review study. The eligibility period is approximately 15 months in duration from 15 July 2014 to 20 October 2015.

8.1.2. Study Period

Each patient’s individual study period for data collection from medical charts is comprised of two main periods as follows:

- **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 anti-TNFα treatment initiation during the eligibility period.

- **Post-Index Event Period:** Begins on the date of index VDZ or anti-TNFα treatment initiation during the eligibility period and ends at the earliest of death, lost to follow-up or date of chart abstraction initiation.

Assuming a data abstraction initiation date of 20 April 2016, and a study eligibility period starting 15 July 2014 and ending 20 October 2015, the design permits a minimum study follow-up period of six months and maximum of 21 months post-index event.

See Figure 1 for an overview of the eligibility and study periods.
Figure 1. Overview of Study Design

Study Period for Data Collection

Eligibility Period for Patient Inclusion

Date of Diagnosis of UC/CD

15 July 2014
VDZ Uptake at Study Sites

20 Oct 2015

Date of Chart Abstraction Initiation
20 April 2016

Pre-Index Event Period
Patient A
Post-Index Event Period

Index Event (Tx Initiation)

Pre-Index Event Period
Patient B
Post-Index Event Period

Index Event (Tx Initiation)

Abbreviations: CD, Crohn’s disease; Tx, treatment; UC, ulcerative colitis; VDZ, vedolizumab
8.2. Site Selection

Approximately 19 centres that treat patients with UC and CD with VDZ and anti-TNFαs will be targeted for enrolment 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, institution size and type (e.g., hospital vs. office-based).

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. Clinical sites will be assessed based on availability of naïve VDZ patients, since this is a population of interest and may be difficult to get adequate sample due to the nature of the uptake of a new treatment, such as VDZ, in real-life clinical practice.

8.3. Patient Population

The patient population is comprised of two distinct treatment cohorts:

1. **VDZ Cohort**: Patients with UC or CD who have initiated VDZ (either biologic naïve or with one prior anti-TNFα treatment) during the eligibility period.

2. **Anti-TNFα Cohort**: Patients with UC or CD who have initiated an anti-TNFα treatment (adalimumab, golimumab [UC only]) and infliximab) (either biologic naïve or with one prior anti-TNFα treatment) during the eligibility period.

8.3.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to be enrolled into the study:

1. Patient has a diagnosis of UC or CD documented in the medical chart.

2. Patient received at least one dose of VDZ or an anti-TNFα (infliximab, adalimumab, or golimumab [UC only]) during the eligibility period (15 July 2014 to 20 October 2015).*

3. Patient was 18 years of age or older at the time of treatment initiation with VDZ or anti-TNFα (index event).

4. Patient was biologic naïve OR had only one prior anti-TNFα treatment at time of index event.

*Note:

- Patients who initiated VDZ and switched to an anti-TNFα during the eligibility period will comprise the VDZ cohort only and will not be included in the anti-TNFα cohort.

- Patients who initiated an anti-TNFα and switched to VDZ during the eligibility period will comprise the VDZ cohort only and will not be included in the anti-TNFα cohort.

- Patients in the anti-TNFα cohort who initiated more than one eligible anti-TNFα during the eligibility period will have only their first eligible anti-TNFα regimen selected as the index event and included in the study.
8.3.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Patient received VDZ OR anti-TNFα as part of an interventional clinical trial ever in their lifetime (includes index treatment).
2. Patient’s index treatment was an anti-TNFα therapy other than infliximab, adalimumab, or golimumab [UC only]. (only applicable to the anti-TNFα cohort)
3. Patient had more than one anti-TNFα treatment prior to index event.
4. Patient initiated index treatment as combination therapy with two biologic agents.
5. Patient received previous treatment with biologic agents for conditions other than IBD ever in their lifetime.
6. Patient’s medical chart is empty or missing.

8.4. Patient Selection

8.4.1. Sampling Frame Identification

All patients 18 years of age or older with UC or CD who initiated treatment with VDZ or one of three anti-TNFα (infliximab, adalimumab, or golimumab [UC only]) treatments during the eligibility period (15 July 2014 to 20 October 2015) (index event) and were biologic naïve or had one prior anti-TNFα treatment at time of index event will be identified at each of the study sites. These patients will comprise the sampling frame. Site staff will record sampling frame patients into an Excel-based patient disposition log (PDL), where each patient will be assigned a pre-formatted unique study identification (ID) number. For each patient, site staff will indicate age at index event, index treatment type (VDZ, infliximab, adalimumab, or golimumab [UC only]), disease type (UC or CD) and treatment history (biologic naïve or one prior anti-TNFα treatment). The site staff will upload the PDL into the electronic data capture (EDC) system.

8.4.2. Preliminary Target Cohort Selection

From the sampling frame, the EDC system will create the preliminary target cohort of patients at each site by first stratifying patients into two treatment cohorts (VDZ vs. anti-TNFα) and then performing selection within each cohort as follows:

1. **VDZ Cohort**: All patients in the sampling frame who are biologic treatment naïve will be selected by the EDC system for inclusion in the study, and a random sample of patients who had one prior anti-TNFα treatment may be undertaken depending on the volume of available eligible patients to ensure target sample size of 250 patients is not markedly exceeded.

2. **Anti-TNFα Cohort**: A random sample of all sampling frame patients will be undertaken by the EDC system to ensure the target sample size of 250 patients is not exceeded markedly. Since this is a reference cohort to the VDZ cohort, the breakdown of treatment history (biologic naïve vs. one prior anti-TNFα treatment) and disease type (UC vs. CD) will be closely monitored in the EDC system by the CRO during patient screening across the study sites. If the breakdown varies drastically to that of the VDZ cohort, the preliminary target cohort sampling scheme may be modified to ensure distributions do not impact the final
analysis. Sites will be informed of any changes made during patient enrolment which could include oversampling beyond 250 patients.

An initial assessment of the treatment cohorts may be conducted during an interim analysis (approximately one month after initiation of chart abstraction) and results from the initial evaluation of patient characteristics will determine the need for oversampling patients treated with anti-TNFα.

8.4.3. Screening for Eligibility

Site staff will review the medical charts for all patients in the preliminary target cohort to determine patient eligibility. The screening results (i.e., screen failures and non-consent) will be captured in the EDC system. All patients alive at the time of chart abstraction initiation will be approached by site staff to obtain informed consent prior to any data abstraction. Site staff will attempt to call eligible patients who have not responded four times before considering a patient as non-interested in study participation. Patients from the preliminary target cohort who meet eligibility criteria and have provided consent (if applicable) will be enrolled into the final study cohort as subjects.

The patient selection process is represented in Figure 2.
Figure 2. Cohort Identification and Screening for Enrollment

**VDZ Cohort**
All patients 18 years of age or older with UC or CD who initiated treatment with VDZ during the eligibility period (15 July 2014 to 20 October 2015) (index event) and were biologic naïve or had only one prior anti-TNFα treatment at time of index event.

**Anti-TNFα Cohort**
All patients 18 years of age or older with UC or CD who initiated treatment with infliximab, adalimumab or golimumab (UC only) during the eligibility period (15 July 2014 to 20 October 2015) (index event) and were biologic naïve or had only one prior anti-TNFα treatment at time of index event.

**Sampling Frame Identification**
- Recording of Sampling Frame Patients into Patient Disposition Log (PDL)
- Recording of Sampling Frame Patients into Patient Disposition Log (PDL)

**Preliminary Cohort Selection**
- Select All
- Random Sample

**Screening for Eligibility and Enrollment**
- Not Eligible
- Eligible
- Not Eligible

- Not Enrolled
- Informed Consent*
- Not Enrolled

- Informed Consent*
- Enrolled
- Chart Abstraction

*Informed consent will be collected for patients known to be alive at time of chart abstraction initiation
8.5. Data Collection

Pseudonymised data (anonymous to non-site staff) from enrolled subjects’ medical charts will be abstracted by site staff and entered at the site into the electronic case report forms (eCRFs) of the EDC system. The EDC system will be in English and will not be translated to local language. Support with eCRF completion will be available in the local language as necessary.

Over the course of the study, the patient study status 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.

8.5.1. Sample Size

The target sample size is 500 patients with a confirmed diagnosis of UC or CD.

- 250 patients treated with VDZ
- 250 patients treated with an anti-TNFα (originator or biosimilar products with market authorisation)

8.5.2. Data Source

The source for all data collected will be the patients’ medical charts. Retrospective data will be abstracted from the medical charts of patients and entered into an EDC system by the trained local site staff.

8.5.3. Study Variables

Variables including but not limited to the following will be collected if available:

- Demographics and medical history
  - Sex
  - Height
  - Weight\(^8\)
  - Smoking status (never, former, current, unknown including number of years smoked, number of packs smoked per day)

- Disease characteristics
  - IBD diagnosis characteristics
    - Age at first-ever diagnosis with IBD (UC or CD diagnosis)
    - Date of first-ever diagnosis
    - Type of IBD (CD vs. UC)
  - UC characteristics

\(^8\) Patient’s BMI will be derived from height and weight measurements.
- At diagnosis and most recent prior to index event (including dates of documentation)
  - Location of UC

  o CD characteristics
    - At diagnosis and most recent prior to index event (including dates of documentation)
      - Location of intestinal involvement
      - Disease behaviour
      - Active fistulae status

- Systemic drug therapy history
  o Non-biologic drug therapies
    - Within 2 years prior to the index event
      - Therapy type, start date, end date/ongoing status at index event
  o Prior anti-TNFα regimen (only for subjects not biologic treatment naïve at time of index event)
    - Anti-TNFα type, type of drug (originator product or biosimilar), reason for initiating treatment, date of initiation and discontinuation, reason for discontinuation, dose escalation/increase status for more than one administration
    - Timing/frequency of dose administration, start date, dose, dose unit (mg, mg/kg), location

- Laboratory measures
  o Within 1 month prior to index event and during post-index event period (including dates of tests)
    - C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), faecal calprotectin (FCP), faecal lactoferrin

- Disease activity and treatment response
  o UC disease activity
    - Assessment closest to the date of IBD diagnosis (within six months post-diagnosis), closest to the date of index event (within six months prior to index event), and all assessments during the post-index event period (including dates of all assessments)
      - Mayo score [0–12], and the sub-scores of domains of the total Mayo score: stool frequency, rectal bleeding, physician global assessment
  o CD disease activity
    - Assessment closest to the date of IBD diagnosis (within six months post-diagnosis), closest to the date of index event (within six months prior to index event), and all assessments during the post-index event period (including dates of all assessments)
- Simple Endoscopic Index for Crohn's Disease (SES-CD) score [0–56], Harvey-Bradshaw Index (HBI) score [0–16], Crohn’s Disease Activity Index (CDAI) score [0 to >450], and the sub-scores of domains of the total CDAI and the HBI scores: general well-being, abdominal pain, abdominal mass, number of liquid/soft stools per day (day before assessment), number of liquid/very soft stools in one week, complications, physician global assessment

  - UC and CD treatment response
    - Assessments during the post-index event period (including dates of all assessments)
      - Complete response, partial response, stable disease (remission), no response, response not assessed and unknown.

  - Diagnostic evaluations related to UC or CD during post-index event period
    - Assessment closest to the date of IBD diagnosis (within six months post-diagnosis), closest to the date of index event (within six months prior to index event), and all assessments during the post-index event period (including dates of all assessments)
      - Type of diagnostic evaluation (e.g., laparoscopy, colonoscopy, sigmoidoscopy), date and reason for procedure, endoscopic findings, and diagnostic evaluation results

- Comorbid medical conditions
  - Comorbid medical conditions (includes: chronic conditions, acute events, reactions to prior treatment and extra intestinal manifestations) within 12 months prior to index event and pre-existing at time of index event
    - Type of comorbidity
  - New-onset comorbid conditions (chronic and acute) during the post-index event period
    - Type of comorbidity and date of diagnosis

- VDZ or anti-TNFα index treatment
  - Treatment overview
    - Type of index treatment, type of drug (originator product or biosimilar), date of initiation, weight (closest to the start of treatment), steroid dependency status at start of treatment, reason for selecting treatment
  - VDZ/anti-TNFα treatment plan
    - Planned timing/frequency of dose administration⁹, planned dose, dose unit (mg, mg/kg), planned location (e.g., hospital outpatient, clinic, home)
  - Modifications to VDZ/anti-TNFα treatment plan

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⁹ Planned Timing/ Frequency of Dose Administration: Week 0 (first dose), Week 2 (after first dose), Week 4 (after first dose), Week 6 (after first dose), Week 8 (after first dose), Week 10 (after first dose), Week 14 (after first dose), Every week, Every other week, Every 4 weeks, Every 6 weeks, Every 8 weeks, other, Unknown.
- Modification type (e.g., dose change only, frequency change only), date of modification, new timing/frequency, new dose, new dose unit (mg, mg/kg), new location, primary reason for modification/discontinuation

- Biologic drug therapy switching (only for subjects who discontinued index VDZ/anti-TNFα treatment during post-index event period)
  - Biologic type, type of drug (originator product vs. biosimilar), date of initiation, date of discontinuation, reason for discontinuation

- Concomitant non-biologic drug therapies during the post-index event period
  - Type of concomitant non-biologic drug therapy, start and end dates, dose, dose unit, frequency, route of administration (ROA), reason for modifications/discontinuation

- Adverse events during VDZ and anti-TNFα therapy
  - All AEs regardless of seriousness or relation to index therapy from date of index event to 18 weeks post-treatment discontinuation or date of chart abstraction initiation (whichever occurs first)
    - Type of AE, whether subject also had this AE within 12 months prior to initiation of VDZ or anti-TNFα, severity, AE seriousness criteria assessment, documented relation to index drug noted in chart, date of onset and resolution, action taken with VDZ or anti-TNFα therapy, and outcome.

- Healthcare resource utilisation
  - Work status
    - Status at date of index event and changes during the post index event period
      - Date of documentation and status (e.g., retired, full-time employee)
  - Healthcare professional (HCP) visits/referrals related to UC or CD management
    - All UC/CD related HCP visits during the post-index event period
      - Type of HCP, type of visit (referral or visit), date and reason for visit
  - ED visits and hospitalisations for any reason (includes UC/CD related reasons and non-UC/CD related reasons)
    - All ED visits and hospitalisations within one year prior to index event and during the post-index event period
      - Type of visit (ED vs. hospitalisation), date of visit/admission and discharge, primary reason for visit, admission to and days spent in intensive care unit (ICU)
  - Surgical procedures related to UC or CD
    - All UC/CD-related surgical procedures during the pre-index event period and the post-index event period
- Type of surgical procedure, date and reason for procedure, and status of complications due to the surgical procedure that resulted in the onset of a medical condition

- 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

### 8.6. Data Management

#### 8.6.1. Data Collection

The CRO will provide a web-based EDC system to serve as an integrated, transparent tool to collect and manage data and track study progress at the centre and patient level. The EDC system will be used for this study for the sites to enter data into. Data in the EDC system are kept in a central location and all data will be transmitted to a central database.

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, except for authorised representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

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 signed-off on electronically by the study investigator or by an authorised staff member to attest that the data contained on the eCRFs are correctly recorded.

In the present case, the source documents are the patient 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 submission of data and responding to data queries. All sites will be assumed to enter case report form (CRF) data via the EDC system.

The EDC system includes logical checks to prevent data entry errors. Data inconsistencies outside the logical checks will be managed by manual queries issued directly to the site. All queries will be monitored until resolution within the EDC through the electronic query report.

#### 8.6.2. Data Monitoring

The CRO will supervise and monitor pseudonymised data abstraction by site staff into the EDC system. The structure and programming of the EDC system permits the CRO to monitor the data closely as the study data accrue.

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. As early as possible, but prior to data base lock, data queries will be identified and resolved.
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 informed consent form (ICF) procedures and documentation exist, ensure regulatory compliance, and perform source document verification.

### 8.6.3. Data Cleaning

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). Queries will be recorded within the EDC system issued electronically to sites for resolution, as early as possible, but before the database locking. There will be no formal source data verification (SDV) as data will be pseudonymised (anonymous to all non-site personnel).

### 8.6.4. 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), all original signed ICFs (if applicable), source documents and 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 according to local regulations, or as specified in the Site Contract Agreement, whichever 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.

### 8.7. Data Analysis

A statistical analysis plan (SAP) will be developed that defines all analytic populations and sub-populations, including definition of treatment history (biologic naïve vs. one prior treatment), response and clinical effectiveness. The SAP will further provide a detailed description of analyses to be performed, and describe methods to deal with unknown data and censoring. The final SAP will include (empty) table shells to be populated during the final data analysis.

An interim analysis will be performed sometime shortly after the first month of data collection. The analysis will aim to provide an initial evaluation of data quality as well as provide an initial understanding of the VDZ study population. It is anticipated that by this point, a small subset of VDZ patients will have undergone a full chart abstraction. The analysis of this data will examine key study outcomes as well as characterise the sample.

All final analyses will be performed once the data from all patients has been collected in the database, cleaned and database lock has occurred.
Data analysis will be reported in a descriptive manner.

- 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

Treatment patterns will be analysed by index treatment cohort (VDZ vs. anti-TNFα), and then sub-stratified by age, disease type (CD or UC), and treatment history (biologic naïve vs. one prior anti-TNFα treatment). Simple statistical tests will be conducted to test for significant differences between cohorts (e.g., t-tests will be used for continuous variables with a normal distribution, Mann–Whitney tests for variables without a normal distribution and chi-square tests for categorical variables).

**8.7.1. Sample Size/Power Considerations**

A total of approximately 500 patients (250 VDZ and 250 anti-TNFα patients) will be included in the final analysis. This sample size will allow for equal description of both treatment groups (VDZ vs. anti-TNFα). A recent systematic review found a pooled discontinuation rate for anti-TNFα treatment in IBD as being 17% (Lopez et al. 2013). A sample size of 250 per treatment group will provide acceptable precision to assess treatment discontinuation rates of 10% or more (Table 1).

**Table 1. Precision Table Based on Treatment Discontinuation Rates**

<table>
<thead>
<tr>
<th>Sample Size Per Group</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
<th>30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>± 4.8%</td>
<td>± 5.7%</td>
<td>± 6.4%</td>
<td>± 6.9%</td>
<td>± 7.3%</td>
</tr>
<tr>
<td>200</td>
<td>± 4.2%</td>
<td>± 4.9%</td>
<td>± 5.5%</td>
<td>± 6.0%</td>
<td>± 6.4%</td>
</tr>
<tr>
<td>250</td>
<td>± 3.7%</td>
<td>± 4.4%</td>
<td>± 5.0%</td>
<td>± 5.4%</td>
<td>± 5.7%</td>
</tr>
<tr>
<td>300</td>
<td>± 3.4%</td>
<td>± 4.0%</td>
<td>± 4.5%</td>
<td>± 4.9%</td>
<td>± 5.2%</td>
</tr>
</tbody>
</table>

While subgroup sample size targets within treatment cohorts (VDZ vs. anti-TNFα) have not been set, sampling across sites will be monitored closely through the EDC system since the intent is for the breakdown of treatment history (biologic naïve vs. first line anti-TNFα) and disease type (UC vs. CD) to be similar between the two treatment cohorts. Based on current estimates, it is assumed approximately 10% of VDZ patients will be biologic treatment naïve and that the majority will have CD (approximately 60%–70%). Therefore, the study will anticipate the enrolment of similar proportions among both index therapy cohorts. The sampling process may be adjusted as needed.

**8.7.2. Primary Endpoints**

Primary objectives are to describe the sample population, treatment patterns and health resource utilisation in patients with CD and UC following initiation of anti-TNFα therapy. Outcomes will be evaluated at six months, and where data are available, at 12 months post-index event. A brief description of these analyses has been provided below; a detailed description of the analyses will be included in the SAP.
8.7.2.1. Patient Populations

Descriptive statistics will be used to describe the patient sample overall and by treatment cohort (VDZ vs. anti-TNFα). Simple statistics will be used described patients’ demographics (e.g., age, smoking status, body mass index, etc.), treatment histories (i.e., one prior biologic treatment, biologic naïve, etc.) and IBD disease type (UC vs. CD). Simple comparisons will be conducted if data are available.

- For continuous variables: N, mean, SD, minimum, median, maximum and number of missing data
- For categorical variables: frequency and percentage for each level and number of missing data

Statistical significance will be assessed at a 0.05 level. P values will be rounded to four decimal places. P values less than 0.0001 will be reported as <0.0001 in tables. Appropriate tests (e.g., t-test, Mann Whitney-U test and chi-square test) will be used for comparison between cohorts. Sample characteristics will be used to stratify the data into subgroups (i.e., age, diagnosis, treatment, treatment history, etc.); subgroup analyses will be conducted throughout as permitted by the availability of data. Examples of variables used to describe the patients populations have been provided in Table 2 and will be defined further in the SAP.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Assessment Period</th>
<th>Variable Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Years</td>
<td>Index Date</td>
<td>Continuous</td>
</tr>
<tr>
<td>Age group*</td>
<td>18–29</td>
<td>Index date</td>
<td>Categorical</td>
</tr>
<tr>
<td></td>
<td>30–44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45–69</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 70 (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Index date</td>
<td>Categorical</td>
</tr>
<tr>
<td></td>
<td>Female (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodyweight</td>
<td>kg</td>
<td>Index date</td>
<td>Continuous</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt; 18.5</td>
<td>Index date</td>
<td>Categorical</td>
</tr>
<tr>
<td></td>
<td>18.5–25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25–29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never/former/current</td>
<td>Index date</td>
<td>Categorical</td>
</tr>
<tr>
<td>Disease Type</td>
<td>CD</td>
<td>Index date</td>
<td>Categorical</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous biologic treatment</td>
<td>Yes/No</td>
<td>Prior to Index Date</td>
<td>Categorical</td>
</tr>
<tr>
<td>Time from IBD diagnosis to index event</td>
<td>Years</td>
<td>Any time prior to index date</td>
<td>Continuous</td>
</tr>
<tr>
<td>Number of comorbid conditions</td>
<td>Any of the listed (see list above)</td>
<td>Any time within 12 months prior to index date (and ongoing at time of index event for chronic conditions)</td>
<td>Categorical</td>
</tr>
<tr>
<td>Updated Charlson Comorbidity Index (comorbidities)</td>
<td>Number</td>
<td>Any time within 12 months prior to index date (and ongoing at time of index event for chronic conditions)</td>
<td>Continuous</td>
</tr>
<tr>
<td>Duration of non-biologic therapies</td>
<td>Years</td>
<td>Within 2 years of index date</td>
<td>Continuous</td>
</tr>
<tr>
<td>Surgery</td>
<td>Yes/ No</td>
<td>Pre-Index event period</td>
<td>Categorical</td>
</tr>
</tbody>
</table>

*Appropriate age groups will be formed upon inspection of the age distribution of the population.
8.7.2.2. 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 and frequency of dose intervals
- Modifications to planned treatment, such as:
  - Comparison of actual vs. planned doses of treatment
  - Comparison of actual vs. planned frequency of treatment
  - 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 with no subsequent therapy
- Discontinuation of index therapy with subsequent implementation of another biologic therapy (VDZ, infliximab, adalimumab or golimumab [UC only]);
  - Switch to either VDZ, infliximab, adalimumab or golimumab [UC only]
  - Reason for switching

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

8.7.2.3. 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. 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])
- 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. Considering that some patients may only have six months of available data, it is possible that most patients may not have experienced the event, in which case the mean or median time to event might not be expressed.

8.7.2.4. Healthcare Resource Utilisation (HRU)

All HRU will be measured during the post-index event period (from index event through chart abstraction date) and will be captured from charts. HRU will be summarised for HCP visits (e.g., internist, GP, dietician, psychologist, psychiatric and surgeon), ED visits, inpatient hospitalisations and
surgical procedures. The number and proportion of patients who experience healthcare utilisation will be investigated in the context of the available follow-up time. The mean number of each outcome of healthcare resource use per patient (both amongst all patients, and amongst only those who experience ≥ 1 use) will also be reported. The outcomes related to healthcare resource utilisation which will be investigated are:

- HCP visits, referrals and types of visits
- HCP visits associated with UC/CD related surgical complication
- Hospitalisations and ED visits
- Admissions to ICU
- Hospital days and ICU days
- Number of planned versus unplanned hospital visits
- Surgical procedures (pre- and post-index event period)

Subgroup analyses will be conducted as permitted by availability of data.

8.7.3. Secondary and Exploratory Endpoints

Secondary objectives are to describe the clinical effectiveness, productivity loss and safety-related outcomes among patients with CD or UC with patients initiating a biologic therapy. Clinical effectiveness will be evaluated at six months and productivity loss and safety outcomes will be evaluated throughout patients’ post-index event period. As an exploratory objective, clinical effectiveness will also be evaluated at 12 months for patients where adequate follow-up data is available. All analyses will be stratified by previously defined subgroups where data are available. A brief description of these analyses has been provided below; additional details will be described in the SAP.

8.7.3.1. Clinical Effectiveness

Clinical effectiveness will be defined by changes in disease measures and outcomes from diagnostic procedures conducted closest to the date of IBD diagnosis, 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. The same analyses will be conducted on the sub-set of patients with 12 or more months based on data availability. 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, SES-CD, HBI, or CDAI and 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, faecal lactoferrin
- Changes based on the evaluation of outcomes associated with diagnostic procedures such as endoscopic findings or other qualitative outcomes provided by HCPs
Treatment response will also be evaluated at six months post-index event and, if available, at 12 months. 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., disease type and treatment history) dependent on data availability.

8.7.3.2. Productivity Loss

Patients with available data will be characterised in terms of employment status at index date (employed vs. not) and changes in employment status over the post-index event period.

For any patients classified as employed at any time over the post-index period, the sum of all days the patient is hospitalised during this period will be calculated. Using publically available data for average salaries based on sex and age, an estimated loss of productivity due to hospitalisations during the post-index period will be calculated for each employed patient based on their days hospitalised multiplied by their age-based average daily salary.

Productivity loss will be described across treatment cohorts and by subgroups (i.e., age, sex, disease type and treatment history) dependent on data availability.

8.7.3.3. 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 versus 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 anti-TNFα initiation to 18 weeks post-treatment discontinuation. For subjects who are not 18 weeks 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 finalised in the SAP.

8.8. 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 and is validated. 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 controlled via a hierarchical user-name and password control. Subject data will be pseudonymised 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 pseudonymised 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.

8.9. 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.

This study may not be fully representative of the whole eligible patient population due to selection bias. It may be possible that not all eligible patients provide informed consent and it may also be possible that sites included in the study may not be fully representative of usual care patterns of UC and CD in Germany. Additionally, patient identification (sampling process) 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 and institution type to increase generalisability of the data. In addition, local site staff will be used to consent patients, which should reduce the rate of non-consent and the patient identification will be documented and monitored by the CRO to reduce this risk of bias.

Subgroup analyses by treatment history (biologic naïve vs. one prior anti-TNFα) and disease type (UC vs. CD) 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 enrol these patients.

Similarly, due to the chart review study paradigm, applying 1:1 matching techniques to conduct a comparative analysis between VDZ and anti-TNFα 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 anti-TNFα 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.

9. PROTECTION OF HUMAN SUBJECTS

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

- Independent Ethics Committee (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, as well as with scientific purpose, value and rigor and will follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) 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 Pharmacoepidemics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organisations 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.

9.1. Informed Consent Procedures

Due to the pseudonymised nature of data collection and to comply with German regulations for conducting research in human subjects, informed consent will be sought for all alive patients identified for participation in the study. Informed consent will be obtained by site study staff prior to enrolment of each patient and data chart abstraction. 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.

9.2. Participant Confidentiality

All data collected in this study will be strictly confidential in accordance with European and German regulations, such as the EU Data Protection Act. Personnel from the following organisations 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 pseudonymised 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 German or EU-wide regulations, such as the EU Data Protection Act.
Explicit consent for the processing of personal data will be obtained from the participating patients before collection of data, and such consent should also address the transfer of the data to other entities (i.e., CRO).

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

9.3. Ethics Committee Review

Before study initiation, the protocol will be submitted for review and approval to the appropriate Central and/or Local Ethics Committee(s) (CEC/LEC) or equivalent group charged with this responsibility in Germany. With assistance from the CRO, each Principal Investigator will be responsible for obtaining the necessary approval from the CEC/LEC and for ensuring that the study complies with local legislation relating to data protection and privacy. When local approval is obtained, the documentation indicating the Ethics Committee's approval or favourable opinion and the names and qualifications of the Ethics Committee members must be sent by the Principal Investigator to the CRO who will send to the study Sponsor before the recruitment process begins.

10. SAFETY MONITORING AND REPORTING

All AEs (serious and non-serious) regardless of the documented relationship to index treatment that occurred from the time of VDZ/anti-TNFα treatment initiation to the earliest of 18 weeks post-treatment discontinuation or date of chart abstraction initiation will be collected and entered by local site staff into the EDC system. AEs collected in the EDC system to address study outcomes will be systematically identified and summarized in the final study report.

If during the course of the study a member of the research team (CRO/Sponsor) becomes aware of an AE related to VDZ (also known as an adverse drug reaction [ADR]) that does not address study outcomes, through spontaneous report (should this occur), such information will be reported within one business day of awareness to the local Sponsor Pharmacovigilance department in Germany.

AEs that do not address study outcomes do not need to be systematically searched and abstracted from patient medical charts. Safety reporting for drugs other than VDZ will follow local standard reporting requirements and fall outside of this protocol.

10.1. Definition of Adverse Drug Reactions (ADRs)

An adverse drug reaction (ADR) is a response to a medicinal product that is noxious and unintended. This includes adverse reactions that arise from the following:

- The use of a medicinal product within the terms of the marketing authorisation
- The use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors
  - Occupational exposure

The definition of an ADR implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An ADR, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For the purposes of this chart review study an AE will be considered an ADR if there is explicit medical chart documentation that the AE was related to treatment.
10.2. Adverse Event Causality

The causal relationship between the index treatment and the AEs will be assessed solely based on explicit medical chart documentation of an AE being related to index treatment.

10.3. Safety Reporting to Regulatory Authorities

The Sponsor will notify regulatory agencies of ADRs in accordance with local regulatory requirements in Germany.

11. PLANS FOR DISSEMINATING & COMMUNICATING STUDY RESULTS

The study team plans on disseminating 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.
12. REFERENCES


ANNEX 1:

LIST OF STAND-ALONE DOCUMENTS
### List of Stand-alone Documents

<table>
<thead>
<tr>
<th>Number</th>
<th>Document Reference Number</th>
<th>Date</th>
<th>Title</th>
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ANNEX 2:

PROTOCOL SIGNATURE PAGE
Investigator Protocol Signature Page

**Protocol Title:** A Retrospective Observational Study to Describe Treatment Patterns, Healthcare Resource Utilisation, Effectiveness and Safety of Vedolizumab (VDZ) and Anti-TNFα in Patients Diagnosed with Crohn’s Disease (CD) or Ulcerative Colitis (UC) in Real-world Clinical Practice in Germany

**Protocol Number:** Vedolizumab 5019

**Protocol Version or Date:** 27 April 2016; Version 2.0

I have reviewed the content of this protocol and agree to participate in the study and adhere to all regulations that govern the conduct of this study.

Site Principal Investigator Name: ____________________________

Site Address: ____________________________

______________________________

______________________________

______________________________

Site Principal Investigator's Signature

Signature Date