Title: A Study to Evaluate Disease Control and Treatment Pattern in Participants With Moderate to Severe Inflammatory Bowel Disease (IBD) in Real Life Practice (INTENT)

NCT Number: NCT03532932

Protocol Approve Date: 28 October 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-Interventional Study Protocol

Title: **INTENT** - **I**nternational, Multicentre, **N**on-Interventional **S**tudy **T**o Evaluate Disease **C**ontrol And **T**reatment Pattern In Patients With Moderate To Severe Inflammatory Bowel Disease In Real Life Practice.

Study ID: IBD-5005 (MACS-2017 - 102279)

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Study phase: Non-interventional Company Sponsored Study

Date: 28 October 2019 **Amendment Number:** 3

Amendment History: 3

Date	Amendment Number	Amendment Type	Region
09 February 2018	Initial Protocol	Not applicable	Russian Federation, Republic of Belarus, Republic of Kazakhstan
22 June 2018	1	Substantial	Russian Federation, Republic of Belarus, Republic of Kazakhstan
22 October 2018	2	Substantial	Russian Federation, Republic of Belarus, Republic of Kazakhstan
28 October 2019	3	Substantial	Russian Federation, Republic of Belarus, Republic of Kazakhstan

1 Administrative information

1.1 Contacts

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

Issue	Contact information
Serious adverse event and pregnancy reporting, the Russian Federation	PI
Serious adverse event and pregnancy reporting, the Republic of Kazakhstan	PI
Serious adverse event and pregnancy reporting, the Republic of Belarus	PI
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PI

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 non-interventional study protocol and also in accordance with the following:

The ethical principles that have their origin in the Declaration of Helsinki [32]; Guidelines for Good Pharmacoepidemiology practices (GPP) [19]; Guidelines on Good Pharmacovigilance Practices (GVP) [20]; All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

SIGNATURES

PI

2 Study summary

Title of the Study

INTENT - **I**nternational, Multicentre, **N**on-Interventional **S**tudy To Evaluate Dise**a**se Co**n**trol And **T**reatment Pattern In Patients With Moderate To Severe Inflammatory Bowel Disease In Real Life Practice.

Study sites

Number of sites: about 35 investigational sites from the Russian Federation, the Republic of Belarus and the Republic of Kazakhstan.

Identification of centres for participation in the study will be based on the assessment of medical centres and hospitals that conduct clinical observation of patients with Inflammatory Bowel Disease (IBD).

Objectives

The purpose of this study is to collect information regarding the real life practice of moderate to severe IBD management in the Russian Federation, the Republic of Belarus and the Republic of Kazakhstan: to document treatment patterns and treatment outcomes in patients with IBD including particularly on the use of available biologic therapies.

Primary objective:

- To characterize the treatment patterns associated with biologics agents use or non-biological therapy (i.e. 5-ASA, immunosuppressive agents (including azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), cyclosporine A), corticosteroids) in patients with moderate to severe Ulcerative Colitis (UC) and moderate to severe Crohn's Disease (CD).

Secondary objectives:

- To characterize patients treated with biologics or/and non-biological treatment (i.e. 5-ASA, immunosuppressive agents (including azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), cyclosporine A), corticosteroids) in terms of demographics, medical, and treatment histories;
- To evaluate and describe the implementation and achievement of Treat-to-target (T2T) goals in real-world clinical practice in moderate to severe IBD patients treated by biological and non-biological therapy during 2 years before enrolment and 1 year observational period after enrolment by treatment type 1) to assess the extent to which proposed Treat to Target goals are achieved in moderate to severe UC/CD patients 2) to describe how and when UC/CD disease activity is assessed 3) to evaluate the potential challenges to achieving T2T targets during routine care ;

- Establish the impact on healthcare resources utilization for patients with moderate to severe UC and CD

Safety Objective:

- To describe the incidence of real-world safety data occurred during 12-months treatment period within routine clinical practice by treatment type (biologics or non-biological IBD therapy) and treatment history (biologic treatment naïve or with prior biological treatment).

Exploratory objective:

- To assess TB in moderate to severe IBD patients receiving biologics and/or non-biological treatment.

Methodology

Study Design**:** International, multicentre, non-interventional retrospective and prospective study.

Study plan: The definition of a Non-Interventional study is provided in Guidelines for Good Pharmacovigilance Practices (GVP) of Eurasian Economic Commission No. 87 [20]. During participation in the study patients are observed according to the local routine practice. The assignment of a particular therapeutic strategy to the patient including all diagnostic procedures is decided in accordance with Clinical recommendations of the Russian gastroenterological association and association of coloproctologists of Russia on the diagnosis and treatment of ulcerative colitis and Crohn's disease; Clinical Protocols of diagnosis and treatment of ulcerative colitis and Crohn's disease in the Republic of Kazakhstan and Clinical Protocol "Diagnosis and treatment of patients with diseases of the digestive system", Appendix 3 in the Republic of Belarus and local routine practice [6-10]..

Number of patients

Approximately 2000 patients will be enrolled in the study.

Diagnosis/Disease/Condition and main criteria for inclusion

Inclusion criteria:

1. Male and female patients 18 years or older by the time of enrolment
2. Confirmed diagnosis of Crohn's disease or ulcerative colitis for at least 2 years prior to enrolment in the study.
3. The presence of a moderate to severe IBD flare at the time of enrolment or in patient anamnesis within 2 years before enrollment treated with steroids or/ and immunosuppressive agents or/ and biologic therapy. IBD flare(s) must be confirmed in the source documentation.
4. Current treatment with steroids or/ and immunosuppressive agents or/ and 5-ASA or/ and biologic therapy
5. Written informed consent, signed before the participation in the study begins.

Exclusion criteria:

Any patient who meets any of the following criteria will not be qualified for entry into the study:

1. Current or previous (within the last two years) indeterminate or not classified colitis.
2. Changing of IBD type in anamnesis (i.e. from UC to CD, etc.) within the last two years.
3. Current, previous (within the last two years) or planned (for the next one year) participation in interventional clinical trial.
4. Presenting of mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
5. Any other condition, which on the opinion of the investigator may impact the patient's participation in the study.
6. Patient received previous treatment with biologic therapy/immunosuppressive agents for conditions other than IBD ever in their lifetime.

Duration of data collection per patient

Data collection per patient will be carried out within the framework of the routine practice. Due to the non-interventional study design it's not possible to appoint exact times for the study visits, although it is expected that the period of observation will be approximately 12 months. The frequency of the visits will be assigned by each physician according to their routine practice. It is anticipated that the patients will visit their physician at least every 6 months; information for the study will be collected from 3 patients' visits to the physician.

Criteria for evaluation

Population descriptors

The main assessments, which will be performed in the study, are presented in the table below.

Assessment / Procedure	Retrospective data collection*	Baseline visit (V1, Day 1)	Observational visit (V2, Month 6)	Final visit (V3, Month12)
Informed consent		X		
Patients' eligibility assessment: Inclusion/exclusion criteria		X		
Date of visit		X	X	X
Demographics data		X		

Disability		X		
Physical examination		X	X	X
Medical history / Concurrent medical conditions	X	X		
History of IBD	X	X		
IBD family history		X		
IBD assessment	X	X	X	X
Disease activity data		X	X	X
IBD status		X	X	X
Laboratory and instrumental evaluation of IBD **	X	X	X	X
IBD treatment	X	X	X	X
Healthcare resources utilization	X	X	X	X
Concomitant treatment		X	X	X
Physician Survey		X		X
Adverse events			X	X

* Retrospective data within two years before of patient enrolment in the study will be collected at Visit 1 after the signing of the informed consent form

**All examinations (laboratory tests and instrumental exams) are done in accordance with clinical routine practice and physician's decision. All examinations results should be registered in electronic CRF only if they are done in routine practice.

Outcomes

The following outcomes will be evaluated in this study separately for UC and CD patients, within each group for subgroups of patients on biologic and non-biological therapy. Study outcomes will be analysed separately for the patients achieved and not achieved clinical remission during the study.

Primary outcomes:

- Distribution of treatment patterns used in patients with moderate to severe UC and with moderate to severe CD treated with biologics. Treatment patterns will be evaluated within 2 years before enrolment – retrospective data and one year after enrolment- prospective data and will include name and type of drug (original product or biosimilar) and treatment regimen including modifications.
- Distribution of treatment patterns used in patients with moderate to severe UC and with moderate to severe CD treated with non-biological treatment. Treatment patterns will be

evaluated within 2 years before enrolment – retrospective data and one year after enrolment-prospective data and will include treatment regimen including modifications.

Secondary outcomes:

- Distribution of socio-demographic variables in patients with moderate to severe UC/ CD treated with biologics or/and non-biological treatment.
- Distribution of clinical variables in patients with moderate to severe UC/ CD treated with biologics or/and non-biological treatment. Clinical characteristics include family history of IBD, smoking habits (no smoker, ex-smoker and current smoker), medical history comorbidities, disease characteristics (age of disease onset, location of disease, clinical course, disease severity, intestinal and systemic (extraintestinal) manifestations, complications in history and during the study observational period, etc).
- Description of methods used for documentation of disease activity in routine practice (incl. clinical, endoscopic, lab, histological), and frequency of objective CD/UC disease activity assessment using different methods.
- Percentage of moderate to severe IBD patients achieved clinical and combined clinical and endoscopic remission (based on T2T definitions).
  - Percentage of patients with moderate to severe IBD with at least one episode of failure of biological therapy or/and non-biological therapy (e.g., dose escalation of biologics, switching to another therapy, IBD-related surgery, medication augmentation).
- Patterns of treatment decisions\actions made after making the clinical assessment of IBD activity (incl. therapeutic de-escalation, escalation, without changes) depending on scenario of achievement /non-achievement of T2T treatment goals.
- Challenges of implementing a T2T strategy in UC and CD in real clinical practice (incl. clinicians related factors, patient related factors, disease related factors).
- Healthcare resources utilization for patients with moderate to severe UC/ CD: hospitalizations due to complications, IBD related surgeries, disability determination (frequency, percentage of UC and CD patients, who used these healthcare resources) within 2 years before enrolment and during 12-months observational period
- Percentage of UC and CD patients with surgical treatment in 2 years history and during 12-months observational period in frames of this study: indications, types of surgeries, complications.

Safety outcome:

- Patient incidence and type of adverse drug reactions related to IBD treatment occurring during 12-months treatment period within routine clinical practice by treatment type (biologics or non-biological therapy) and treatment history (biologic treatment naïve or with prior biological treatment);
- Patient incidence and type of serious adverse events related to IBD treatment occurring during 12-months treatment period within routine clinical practice by treatment type (biologics or non-biological therapy) and treatment history (biologic treatment naïve or with prior biological treatment).

Exploratory outcomes:

- Number of moderate to severe UC and CD patients with TB positive tests results/active TB before start of biological therapy.
- Number of moderate to severe UC and CD patients with TB reactivation/occurrence in frames of this study by treatment type (biologics or/and non-biological treatment).

Statistical methods

All data from patients enrolled in this study will be analysed. Information on CD and UC patients will be presented separately. Also, analysis will be performed separately by therapy subgroups (patients receiving non-biological therapy and patients receiving biological therapy). Due to complexity of treatment regimen a manual review can be used to define treatment subgroup for each patient.

A descriptive analysis approach will be used to analyse the data and the study outcomes for the different study subgroups.

Descriptive statistics will include summary tables (n, mean, median, standard deviation, minimum and maximum, lower and upper quartile for continuous variables and n, frequency and percentage for categorical values). Proportion will be assessed together with 95% confidence interval, if applicable. Cross tabulations will be used to present study outcomes by the corresponding subgroups, when required. Time to event will be described with Kaplan-Meier estimates. Median time to event will be presented together with the lower and upper quartiles. Baseline and retrospective data will be used to describe the patient population and will be tabulated separately.

The number and percentage of patients who have reached remission while in the study will be presented. Selected outcomes will be reported separately for those who have reached remission and those who haven't. Mayo and HBI scores data will be analyzed according to the scales definitions.

Laboratory data will be reported in terms of frequency and percentage of abnormal findings.

In general, all data will be listed, sorted by type of disease (UC and CD), site and patient number, and when appropriate by visit number within patient.

3 Table of Contents

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4 List of Abbreviations and Definition of Terms

4.1 List of Abbreviations

ADR:	Adverse Drug Reaction
AE:	Adverse Event
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
BMI:	Body Mass Index
CA:	Competent Authority
CD:	Crohn's disease
CER:	Clinical and endoscopic remission
CIS:	Commonwealth of Independent States
CR:	Clinical remission
CRF:	Case Report Form
CRO:	Contract Research Organisation
CRP	C-reactive protein
CV:	Curriculum Vitae
DMP:	Data Management Plan
DSO:	Drug Safety Officer
EC:	Ethics Committee
eCRF:	electronic Case Report Form
ESR:	Erythrocyte Sedimentation Rate
EU:	European Union
FPFV:	First Patient First Visit
FPLV:	First Patient Last Visit (end of enrolment)
GCP:	Good Clinical Practice
GEP:	Good Epidemiologycal Practice
GI:	Gastroenterologist
GPP:	Good Pharmacoepidemiology Practices
GVP:	Good Pharmacovigilance Practices
HCRU:	Health care resource utilisation
IBD:	Inflammatory bowel disease

ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
INN:	International Nonproprietary Name
IRB:	Institutional Review Board
LEC:	Local Ethics Committee
LPLV:	Last Patient Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
NIS:	Non-interventional study
PSUR:	Periodic Safety Update Report
QA:	Quality Asurance
RB:	the Republic of Belarus
RK:	the Republic of Kazakhstan
RF:	the Russian Federation
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SAE:	Serious Adverse Event
SmPC:	Summary of Product Characteristics
SD:	Standrad Deviation
SDV:	Source Data Verification
SPC:	Summary of Product Characteristics
TB:	Tuberculosis
TNFα:	Tumor Necrosis Factor-α
T2T:	Treat to Target
UC:	Ulcerative colitis
WBC:	White blood cells
WHO:	World Health Organization

4.2 Definition of Terms

Inflammatory bowel disease (IBD) - a group of chronic, often relapsing, immunologically-mediated gastrointestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease may involve any portion of the length of the gastrointestinal tract from mouth to anus in a transmural fashion from mucosa to serosa whereas ulcerative colitis primarily affects colonic mucosa and submucosa.

IBD flare - a flare of symptoms in a patient with established CD/UC who is in clinical remission, either spontaneously or after medical treatment. Relapse should be preferably confirmed by laboratory parameters, endoscopy or imaging in clinical practice. The definition of IBD flare (including severity) will be in accordance with Clinical recommendations of the Russian gastroenterological association and association of coloproctologists of Russia on the diagnosis and treatment of ulcerative colitis and Crohn's disease; Clinical Protocols of diagnosis and treatment of ulcerative colitis and Crohn's disease in the Republic of Kazakhstan and Clinical Protocol "Diagnosis and treatment of patients with diseases of the digestive system", Appendix 3 in the Republic of Belarus and local routine practice [6-10].

IBD is a chronic condition that is characterized by intermittent periods of active disease (relapses) and little or no disease activity (remission). The duration and severity of the active period vary widely from person to person. The goal of treatment of IBD is to induce and maintain remission for better outcomes of the disease.

IBD remission – a resolution of symptoms (clinical remission) and mucosal inflammation (endoscopic remission). The definition of IBD remission will be in accordance with Clinical recommendations of the Russian gastroenterological association and association of coloproctologists of Russia on the diagnosis and treatment of ulcerative colitis and Crohn's disease; Clinical Protocols of diagnosis and treatment of ulcerative colitis and Crohn's disease in the Republic of Kazakhstan and Clinical Protocol "Diagnosis and treatment of patients with diseases of the digestive system", Appendix 3 in the Republic of Belarus and local routine practice [6-10].

Biologics dose escalation will include any increase in dose, frequency, or both;

Augmentation with non-biological therapy will be defined as starting a new non-biological drug or increase in dose/frequency of the concurrent non-biological drugs with biological therapy. Non-biological therapies included aminosalicylates, immunomodulators, and corticosteroids;

Switching will be defined as a subset of initial biologic agent discontinuers who initiated another biological therapy;

IBD-related surgery will include but not be restricted to colectomy, ostomy (colostomy or ileostomy), fistula repair, abscess repair, and strictureplasty.

4.3 IBD activity assessment

Validated Mayo score evaluates ulcerative colitis stage, based on four parameters (full Mayo score): stool frequency, rectal bleeding, endoscopic evaluation and physician's global assessment (see **Appendix 3**). Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity). The partial Mayo score uses the three non-invasive components of the full Mayo Score (stool frequency, rectal bleeding and Physician's global assessment). This excludes the score for the endoscopic findings; therefore, the maximum score is reduced from 12 to 9 points. The full or partial Mayo score (in accordance with routine clinical practice) will be evaluated at each study visit.

Harvey-Bradshaw index (HBI) is used in the assessment of Crohn's disease activity (see **Appendix 4**). It is a validated clinical index for CD, including the 5 categories of: general well-being, abdominal pain, number of liquid stools, abdominal mass and complications. The score ranges from 0 to 25 with higher scores indicating higher disease activity. The scores were classified as follows: less than 5 is remission, 5 to 7 is mild, 8 to 16 is moderate, and greater than 16 is severe. HBI will be evaluated at each study visit.

4.4 Treat to target approach in IBD treatment

"Treat to target" approach - evidence- and consensus-based recommendations for selecting the goals for treat-to-target strategies in patients with IBD.A "Treat to target" approach for UC includes clinical remission (defined as resolution of rectal bleeding and diarrhea/altered bowel habit) and endoscopic remission (defined as Mayo endoscopic subscore of 0–1). Biomarker remission (normal C-reactive protein (CRP) and calprotectin) is considered as an adjunctive target. Histological remission is considered as an adjunctive goal [17, 21].

Clinical remission for CD is defined as resolution of abdominal pain and diarrhea/altered bowel habit. Endoscopic remission for CD is defined as resolution of ulceration at ileocolonoscopy or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy. Biomarker remission (normal C-reactive protein (CRP) and faecal calprotectin) is considered as an adjunctive target [14, 21].

Treat to target approach achievement will be evaluated at observational (Month 6) and final (Month 12) visits.

5 Introduction

5.1 Background

Inflammatory Bowel Disease (IBD) consists primarily of two chronic, often relapsing, immunologically-mediated gastrointestinal disorders: ulcerative colitis (UC) and Crohn's disease (CD). CD and UC are chronic gastrointestinal diseases characterized by an exacerbated inflammatory

cell infiltrate in the gut mucosal tissue. Currently IBD present one of the most urgent and complicated problems of gastroenterology. IBD results in irreversible structural and functional defect of intestine, finally leading to patient's incapacity [1, 2, 5].

IBD represents both medical and social challenge. Heterogeneity of clinical course, extra intestinal symptoms, severe complications together with increasing prevalence constitute high urgency of this disease. Ulcerative colitis and Crohn's disease are of chronic relapsing or continuous course, therefore long lasting treatment (including surgery in case of complications) is often required [1-12]. So, patient's life quality is greatly affected. IBD often causes disability and incapacity in young and middle-aged population, patients experience limitation of working and physical capacity, social activity decrease and emotional disturbances.

The primary goal of treating patients with IBD is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function and participation in social and work-related activities. A "Treat to Target" (T2T) strategy has been proposed as an optimized management approach for inflammatory bowel diseases [13, 14, 17, 18, 21].

Existing treatment methods show insufficient effectiveness. Aminosalicylates are only modestly effective; glucocorticoids can cause unacceptable adverse events and do not provide a benefit as maintenance therapy. Tumor necrosis factor (TNF) antagonists, although efficacious, may predispose patients to infections and other serious adverse reactions [3, 4, 6-10, 12, 28, 29]. Besides, a considerable portion of patients do not respond to the treatment with TNF-antagonists (primary non-responders) or will lose response to such therapies over time (secondary loss of response). New biological treatment medication Vedolizumab (Entyvio®) is the first and only gut selective biologic approved medication indicated for the treatment of adult patients with moderate to severe UC and CD, who have had an inadequate response with, lost response to, or were intolerant to either non-biological therapy or a tumor necrosis factor-alpha (TNFα) antagonists [15, 16, 25, 26].

5.2 Rationale

There is no accurate information on treatment patterns used in routine clinical practice for IBD patients in Russia and other CIS countries [3, 6-10, 12]. In connection with this, appropriateness of the large-scale investigation gathering information about disease characteristics, treatment patterns treatment responses and achievement of "Treat to Target" goals in IBD patients of Russia, Belarus and Kazakhstan is evident.

Better understanding of the IBD disease management will help to reveal the gaps, increase treatment goals awareness and improve medical care of patients. This will also allow better understanding of the clinical and economic burden and potential significant unmet need related to anti-TNF therapy in IBD in relative countries. The impact of sub-optimal therapy among IBD patients on health care resource utilization (HCRU) will also be investigated.

6 Study Objectives and outcomes

6.1 Study objectives

The purpose of this study is to collect information regarding the real life practice of moderate to severe inflammatory bowel disease (IBD) management in Russia, Belarus and Kazakhstan: to document treatment patterns, treatment outcomes in patients with IBD particularly on the use of available biologic therapies.

Primary objective:

- To characterize the treatment patterns associated with biologics agents use or non-biological therapy (i.e. 5-ASA, immunosuppressive agents (including azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), cyclosporine A), corticosteroids) in patients with moderate to severe Ulcerative Colitis (UC) and moderate to severe Crohn's Disease (CD).

Secondary objectives:

- To characterize patients treated with biologics or/and non-biological treatment (i.e. 5-ASA, immunosuppressive agents (including azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), cyclosporine A), corticosteroids) in terms of demographics, medical, and treatment histories;
- To evaluate and describe the implementation and achievement of Treat-to-target (T2T) goals in real-world clinical practice in moderate to severe IBD patients treated by biological and non-biological therapy during 2 years before enrolment and 1 year observational period after enrolment by treatment type 1) to assess the extent to which proposed Treat to Target goals are achieved in moderate to severe UC/CD patients 2) to describe how and when UC/CD disease activity is assessed 3) to evaluate the potential challenges to achieving T2T targets during routine care ;
- Establish the impact on healthcare resources utilization for patients with moderate to severe UC and CD

Safety Objective:

- To describe the incidence of real-world safety data occurred during 12-months treatment period within routine clinical practice by treatment type (biologics or non-biological IBD therapy) and treatment history (biologic treatment naïve or with prior biological treatment).

Exploratory objective:

- To assess TB in moderate to severe IBD patients receiving biologics and/or non-biological treatment.

6.2 Study outcomes

The following outcomes will be evaluated in this study separately for UC and CD patients, within each group for subgroups of patients on biologic and non-biological therapy. Study outcomes will be analysed separately for the patients achieved and not achieved clinical remission during the study.

Primary outcomes:

- Distribution of treatment patterns used in patients with moderate to severe UC and with moderate to severe CD treated with biologics. Treatment patterns will be evaluated within 2 years before enrolment – retrospective data and one year after enrolment- prospective data and will include name and type of drug (original product or biosimilar) and treatment regimen including modifications.
- Distribution of treatment patterns used in patients with moderate to severe UC and with moderate to severe CD treated with non-biological treatment. Treatment patterns will be evaluated within 2 years before enrolment – retrospective data and one year after enrolment- prospective data and will include treatment regimen including modifications.

Secondary outcomes:

- Distribution of socio-demographic variables in patients with moderate to severe UC/ CD treated with biologics or/and non-biological treatment.
- Distribution of clinical variables in patients with moderate to severe UC/ CD treated with biologics or/and non-biological treatment. Clinical characteristics include family history of IBD, smoking habits (no smoker, ex-smoker and current smoker), medical history comorbidities, disease characteristics (age of disease onset, location of disease, clinical course, disease severity, intestinal and systemic (extraintestinal) manifestations, complications in history and during the study observational period, etc).
- Description of methods used for documentation of disease activity in routine practice (incl. clinical, endoscopic, lab, histological), and frequency of objective CD/UC disease activity assessment using different methods.
- Percentage of moderate to severe IBD patients achieved clinical and combined clinical and endoscopic remission (based on T2T definitions).
- Percentage of patients with moderate to severe IBD with at least one episode of failure of biological therapy or/and non-biological therapy (e.g., dose escalation of biologics, switching to another therapy, IBD-related surgery, medication augmentation).
- Patterns of treatment decisions\actions made after making the clinical assessment of IBD activity (incl. therapeutic de-escalation, escalation, without changes) depending on scenario of achievement /non-achievement of T2T treatment goals.

- Challenges of implementing a T2T strategy in UC and CD in real clinical practice (incl. clinicians related factors, patient related factors, disease related factors).
- Healthcare resources utilization for patients with moderate to severe UC/ CD: hospitalizations due to complications, IBD related surgeries, disability determination (frequency, percentage of UC and CD patients, who used these healthcare resources) within 2 years before enrolment and during 12-months observational period
- Percentage of UC and CD patients with surgical treatment in 2 years history and during 12-months observational period in frames of this study: indications, types of surgeries, complications

Safety outcome:

- Patient incidence and type of adverse drug reactions related to IBD treatment occurring during 12-months treatment period within routine clinical practice by treatment type (biologics or non-biological therapy) and treatment history (biologic treatment naïve or with prior biological treatment);
- Patient incidence and type of serious adverse events related to IBD treatment occurring during 12-months treatment period within routine clinical practice by treatment type (biologics or non-biological therapy) and treatment history (biologic treatment naïve or with prior biological treatment).

Exploratory outcomes:

- Number of moderate to severe UC and CD patients with TB positive tests results/active TB before start of biological therapy.
- Number of moderate to severe UC and CD patients with TB reactivation/occurrence in frames of this study by treatment type (biologics or/and non-biological treatment).

7 Study Administrative Structure

Contact and responsibilities of all parties contributing to the study, including all investigators, are detailed below.

The sponsor is responsible for all study-related activities including study set-up activities and study documentation development. The responsible CRO for specific study-related activities will perform these activities in full or in partnership with the sponsor.

7.1 Steering Committee

The Steering Committee serves to provide overall supervision of the study activities across the study. The Steering Committee is responsible for composing and evaluating the research/scientific/medical questions and issues; guiding and coordinating; maintaining open and

active communication about the goals, process, and findings of the Study; compiling and editing the final Study Report and study publication.

7.2 Study Sites

The study is planned to be conducted in approximately 35 investigational sites from the Russian Federation, the Republic of Belarus and the Republic of Kazakhstan.

Identification of centres for participation in the study will be based on the assessment of medical centres and hospitals that conduct clinical observation of patients with Inflammatory Bowel Disease.

The study sites will be selected according to following criteria:

- availability of the required patient population - (the sites should treat at least 50 patients with IBD per year).
- appropriate qualification of site staff - availability of gastroenterologists, coloproctologists specialists who work in IBD area;
- ability to perform the data entry proccdures via electronic data system.

The Sponsor/responsible CRO will keep a record of the individuals responsible for each participating Study Site, the Investigators. The chosen Investigators must have qualifications and expertise directly related to the Study.

7.3 Sponsor Personnel

Takeda will keep a record of all relevant Sponsor personnel.

Name and address of the Sponsor:	Takeda Pharmaceutical LLC 2, bld. 1, Usacheva str., Moscow 119048, Russian Federation Phone: + 7 495 933 5511 Fax: + 7 495 502 1625
Name, position, address and telephone of specialist who is responsible for preparation of the protocol	PI

	PI
Name and position of person who responsible for coordinating management of the non-interventional study	PI
Name and position of specialist who is responsible for drug safety on behalf of the Sponsor	PI

7.4 Contract Research Organisation

Summary of tasks delegated to the Contract Research Organization (CRO):

- The study documentation development (Case Report Form, project management plan etc.),
- Study implementation and initiation, study conducting and study close-out,
- Data management,
- Project management,
- Statistical analysis, including the statistical analysis plan,
- Study report development

Every task has more detailed description in the Takeda-CRO contract and the study plans.

The CRO will keep a record of all involved CRO personnel (e.g. CVs of monitors and data manager involved in the study as well as CV and other confirming documentation of the persons who are responsible for database constructing and all the medical operations).

Name, address and telephone of the Contract Research Organization:	tbd
Name and position of person who responsible for project management of the study on behalf of the CRO	tbd

Name and position of person who responsible for drug safety on behalf of the CRO	tbd
Name and position of person who responsible for data management on behalf of the CRO:	tbd
Name and position of specialist who is responsible for statistical strategy and analysis of the study on behalf of the CRO:	tbd
Name and position of specialist who is responsible for quality assurance and quality control on behalf of the CRO:	tbd

7.5 Essential Documents

The following essential documents must be received by the Sponsor before the study is initiated at an investigational site:

- Written agreement between Takeda and CRO;
- Signed and dated institution and investigator contracts;
- Patient Information Sheet and Informed Consent Form in local language (approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) / Regulatory Authorities as locally required);
- Written IEC / LEC/ IRBs / Regulatory Authorities approvals according to local regulations;
- Authority notification according to local regulations.

8 Ethical and Legal aspects

This study is a non-interventional study where the existence of the study has no impact on the patient except for collection of informed consent to use of the patient's data.

Non-interventional studies are covered by the definition presented in the Rules of Good Pharmacovigilance Practice (GVP) Of Eurasian Economic Union (No. 87 of 3 November 2016) [20]. Non-interventional study is a study that meets the following conditions:

–the medicinal product(s) is (are) prescribed in the usual manner according to local routine practice

–the decision to prescribe a specific treatment to a patient is not accepted in advance according to the study protocol, but routine clinical practice, and the administration of the medicinal product is clearly separated from the decision to include the patient in the study;

– no additional diagnostic or control procedures are applied to patients, and

– epidemiological methods are used to analyze the data obtained.

8.1 Ethical conduct of the Study

All the activities during the study to be performed according to the ethical rules and considerations, described in the Declaration of Helsinki (2013, Fortraleza) [32]. This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), Guidelines for Good Pharmacovigilance Practices (GVP), Good Epidemiological Practice requirements and any local regulations [19, 20, 32]. Special attention will be paid to data protection.

Takeda/the responsible CRO will ensure that the protocol, any amendments and the Patient Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/ Institutional Review Boards (IRBs)/ Regulatory Authorities according to local requirements.

Takeda as the Sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/ IRBs/ Regulatory Authorities, if applicable.

8.2 Independent Ethics Committee

According to applicable regulations, the responsible CRO will notify or obtain approval from the relevant IEC of the protocol, any amendments and the Patient Information Sheet / Informed Consent Form (ICF). This protocol, amendments to the protocol, the ICF, and other documents required by all applicable laws and regulations, must be submitted to a IEC for approval. The IEC's written approval of the protocol and patient ICF must be obtained and submitted to the Sponsor or the responsible Contract Research Organisation before start of the study. Documented approval from central IEC will be obtained for all participating investigational sites prior to the study start.

The Sponsor or the responsible CRO will submit required documents to the IEC such as:

- notification of the end-of-study,
- a summary of the study results.

The Sponsor or the responsible CRO will supply relevant documents for submission to the Independent Ethic Committee for the protocol's review and approval.

If necessary, the Sponsor/responsible CRO will get prolongation, change or resumption of approval by IEC. IEC should submit to the Sponsor, at its request, the list of the members of IEC taking part in voting and the confirmation that IEC is organized and is conducting its activities in conformity with the principles of ICH GCP, the principles stated in the Helsinki declaration, the applicable legislation and normative documents.

The Sponsor / responsible CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC and will provide the Investigators with a copy of this list prior to the study start.

8.3 Local Ethics Committee / Institutional Review Board

This non-interventional study will be submitted to Local Ethics Committees (LECs)/ Institutional Review Board (IRB) upon the regulations of the participated countries. LECs should also approve all substantial amendments to the protocol.

If necessary, investigator should get prolongation, change or resumption of approval by LEC/IRB. LEC/IRB should submit to the Sponsor, at its request, the list of the members of LEC/IRB taking part in voting and the confirmation that LEC/IRB is organized and is conducting its activities in conformity with the principles of ICH GCP, the principles stated in the Helsinki declaration, the applicable legislation and normative documents. When necessary, an extension, amendment or renewal of the LEC/IRB approval must be obtained and also forwarded to the Sponsor.

8.4 Regulatory Authority Approvals/Authorizations

Non-interventional (observational) studies are not covered by the definition of the «clinical trials» stated in the EU Clinical Trial Regulation No.536/2014 [23]. A written approval of IEC and (if necessary) of LECs of the sites of NIS to be with the ethical principles of NISs and protection of rights of the patients taking part in it.

Authorities' approval in the Russian Federation

There is no need in permission of other competent authorities (CA) of the Russian Federation for conduction of the present NIS.

The Sponsor will send required documents to the CA and/or other national or regional authorities for their notification. The Sponsor will keep an updated list of submission and notification dates and a copy of all documents submitted.

Authorities' approval in the Republic Kazakhstan

There is no need in permission of other competent authorities (CA) of the Republic of Kazakhstan for conduction of the present NIS.

Authorities' approval in the Republic Belarus

There is no need in permission of other competent authorities (CA) of the Republic of Belarus for conduction of the present NIS.

8.5 Patient Information Sheet and Informed Consent Form

The investigator must have the IEC/IRB written approval/favourable opinion of the written Informed Consent Form and any other written information to be provided to patients/legal representatives prior to the beginning of the study.

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and will be in accordance with all applicable laws and regulations. The informed consent form and patient information sheet describe disclosures of the patient's personal and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given.

In the event the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The informed consent form will detail the requirements of the patient and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care. The patient information sheet and informed consent form must be written in a language fully comprehensible to the prospective patient.

The patient must agree that Sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the patient's data / personal records which were collected, processed and stored in an anonymous form. The patient 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, which may be located in other countries with potentially different regulations for data.

The patient/legal representative 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 (for details, please see the section11.5.).

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

8.6 Signing of Informed Consent Form

The investigator must give the patient/legal representative oral and written information about the study in a form that the patient/legal representative can understand and obtain the patient's/legal representative's written consent before collection of identifiable patient information (hereinafter referred to as personal data).

Before consenting, the patient/legal representative must be provided with ample time to: (1) inquire about details of the study, (2) decide whether or not to participate in the study and (3) consider and to pose questions. Since the study is observational the consent only concerns the data collection per see and is not consent to any interventional procedure or treatment.

If the patient/legal representative determines he or she will participate in the study, then the informed consent form must be signed and dated by the appropriate person, at the time of consent and prior to the patient entering into the study. The patients/legal representatives should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to patient entering into the study.

The original, signed Informed Consent Forms must be kept in the Investigational Site. The another original copy of the signed informed consent form and patient information sheet shall be given to the patient.

8.7 Patient identification

The Patient Information Sheet and Informed Consent Form will explain that study data will be stored in electronic CRF (eCRF) and computer database, maintaining confidentiality. Patients in this database will be identified by unique patient identification code (patient number).

This code is only used for study purposes. After informed consent form is signed every patient is given an identification code. The 5-digit patient identification code consists of:

– 2-digit site number,

– 3-digit patient number; patient will be given as a three-digit figure attributed to the patient (the least available from the pre-designed sequence 001, 002, 003 … etc).

Sites will amount of identification codes via database. The individual electronic Case Report Form (eCRF), specially designed for this study, will be completed for each patient enrolled.

For the duration of the study and afterwards, only Investigator is able to identify the patient based on the identification code. The Investigator must keep a Patient Identification List of all patients that have signed the informed consent form, including patient number, full patient' name, date of birth and date of Informed Consent signing (see section 8.6).

Authorized representative of a competent authority may require direct access to parts of the study site records relevant to the study, including patients' medical records for data verification purposes.

8.8 Patient insurance

In this study treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and, respectively, the institutions involved provide sufficient protection for both patient and physician.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

8.9 Confidential and non-disclosure of personal data

The sponsor and responsible CRO affirm and uphold the principle of the patient's right to protection against invasion of privacy. The personal data of the NIS participants will be kept and processed with observance of the provisions of the RF federal law No. 152 "On personal data", law of the Republic of Kazakhstan "On personal data and their protection" and laws of the Republic of Belarus № 455-3 "On Information, Informatization and Protection of Information" [27, 31]. Throughout this study, a patient's source data will only be linked to the study database or documentation via a unique identification number (see Section 8.7).

The necessary personal data of the patients (for example, demographic parameters) will be gathered solely for achieving the objectives of the NIS, envisaged by its design and the minimal volume. Names, addresses, numbers of medical records/ambulatory record will not be entered into eCRF. No documentation identifying the patients will be disclosed.

The patients' names will not be disclosed to the sponsor. If the patient's name is mentioned in a document, such name should be deleted before submission of the copy/original of the document to the sponsor/responsible CRO. The results of the NIS kept in the electronic form, should be stored in accordance with the laws of information protection.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any competent authority, the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation. Before inclusion in the NIS, the patient will be acquainted with the terms and conditions of confidentiality of using his/her personal data, including the necessity of access to them of the monitor and other authorized persons of the Sponsor. These terms and conditions will be presented in the information for patient. The patient will be included into the NIS only after getting acquainted with the above-mentioned information and signing of the Informed Consent Form.

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e. patient name, address, and other identifier fields not collected on the eCRF).

The investigator will keep the list of the patients' names (Patient Identification List) so that to use it if the patients' primary documentation is needed. If SADR is reported, the representative of the regulatory authorities can ask for additional explanations. In this case the Sponsor is prohibited to contact the patient directly. All additional information will be presented by the investigator.

9 Non-interventional study material management

In accordance with NIS definition and principles of NISs [20] the study medication and concomitant medication cannot be provided by the Sponsor.

10 Study Design and Plan

10.1 Overall study design

This is an international, retrospective and prospective, multicentre, non-interventional, observational study. This study is a 'non-interventional study' as defined in EU Clinical Trial Regulation No. 536/2014 [23] and the guidelines for GVP [21]. This means that:

- the medicinal product(s) is (are) prescribed in the usual manner according to local routine practice,
- the assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice;
- the prescription of the medicine is clearly separated from the decision to include the patient in the study;
- no additional diagnostic or monitoring procedures shall be applied to the patients;
- epidemiological methods shall be used for the analysis of collected data.

A prospective design of the study means that patients that have been enrolled according to criteria inclusion and exclusion and signed the Informed Consent form will be observed in the future.

In the retrospective part of the study all data will be collected from past records of patients' source documents. Retrospective design means that all patients' data that will be collected in the study were recorded in the patients' file prior to the date when Informed Consent form is signed (in scope of investigator's responsibility about data confidentiality and data protection described in the study protocol).

10.2 Study timelines

Milestone	Planned Date
Planned Start of patient enrolment (FPFV)	Q2 2018
Planned End of the enrolment (LPFV)	Q2-Q3 2020
Planned End of the patient observation (LPLV)	Q2 - Q3 2021
Planned End of the study (end of data collection)	Q3 – Q4 2021
Interim data analysis	2019, 2020
Final study report	Q4 2021

Due to the observational design of the study, patient visits to the referring physician are not pre-specified by the study protocol but will follow usual clinical practice. All patient-care decisions, including diagnostic and therapeutic interventions, will be made by and conducted at the discretion of the participating study physicians according to their clinical judgment and the local standard of medical care.

Start of of patient enrolment (First Patient First Visit) is defined as the date of the start of data collection (first patient signed ICF for data collection).

End of the enrolment (Last Patient First Visit) is defined as the date when the last patient signs ICF and enrolled in the study.

End of the patient observation (Last Patient Last Visit) is defined as the last date when the patients are observed in the scope of the study.

End of study (end of data collection) is defined as the date when the last data point is collected. Up to this date all the eCRFs should be completed and all the data clarifications (queries) should be done.

The Sponsor will ensure that End-of-Study notification is submitted to the CA, IEC and LEC/IRB (if applicable). The Sponsor will ensure that results are posted on "clinicaltrials.gov" and as required by local authorities.

The study is considered to be completed after the database is closed, the final statistical analysis is performed, and the study report is written. The study report will be signed within 12 months after the collection of the last data point.

10.3 Discussion of Study Design

The primary study objective is to provide accurate and comprehensive information regarding the treatment patterns associated with biologics use or non-biological therapy in patients with moderate to severe Ulcerative Colitis (UC) and Crohn's Disease (CD) in routine clinical

practice of Russia, Belarus and Kazakhstan. So, the non-interventional study design was chosen as it helps to obtain data in routine clinical practice.

Non-interventional principles defined in the GVP [21] permits to estimate "real life" conditions. Besides non-interventional studies help to analyze big sample sizes without special selection and screening within routine clinical practice. Thus, non-interventional design allows attaining the objective of the study.

The population that is planned to include in the study supposed to be heterogeneous in terms of different types of diseases and clinical characteristics. It is planned to avoid this bias by subgroup analysis.

Retrospective study design was chosen in order to include into analysis a wide range of data in relatively short period of time. This observational retrospective and prospective study design is supposed to allow collecting of data about IBD patients in routine practice on a tight timetable (in comparison with the same duration of prospective part). The retrospective part of the study includes 2 years of data collection. The prospective part includes 1 year of observation and data collection after signing of Informed Consent Form. Prospective part allows to collect the latest patients' data for evaluation of patients' condition.

10.4 The Plan of observation

The investigator gives the patient necessary information about the study and asks the patient to read the Patient Information Sheet and Informed Consent Form. If the patient agrees to participate in the study after having enough time for reading of the ICF and getting all answers about the study, then the patient and the investigator sign the Inform Consent Form and the investigator includes the patient in the study.

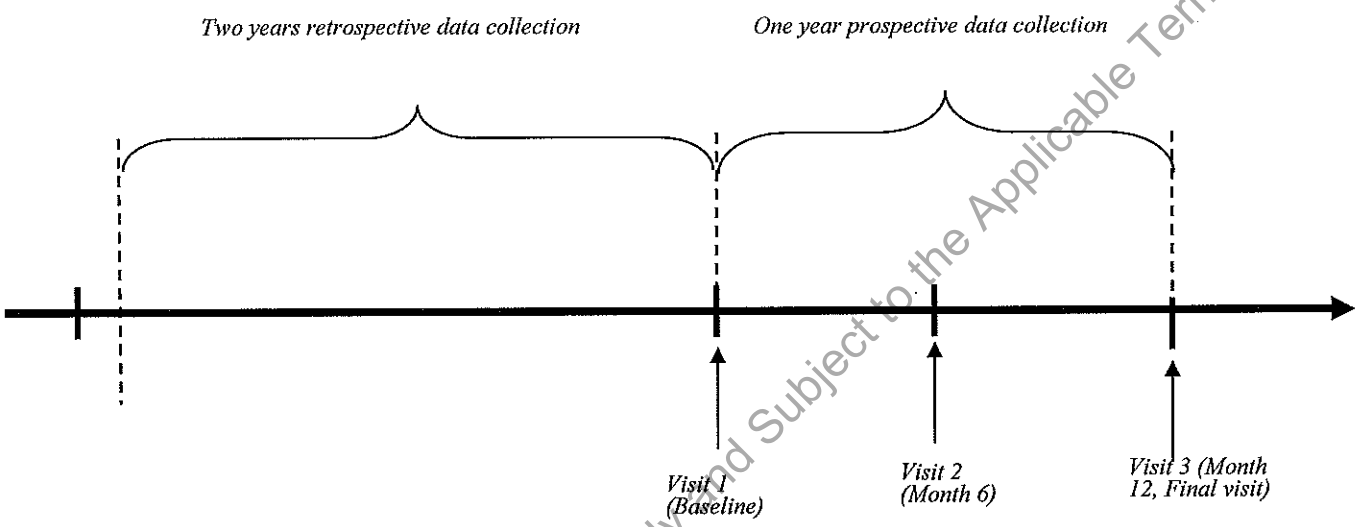
During participation in the study patients are observed according to the local routine practice. The assignment of a particular therapeutic strategy to the patient including all diagnostic procedures is decided in accordance with Clinical guidelines of the Russian gastroenterological Association and the Association of Coloproctologists of Russia on the diagnosis and treatment of ulcerative colitis and Crohn's Disease (Russian Federation), Clinical Protocols for Diagnosis and Treatment of ulcerative colitis and Crohn's Disease (Republic of Kazakhstan) and Clinical Protocols for Diagnosis and treatment of patients with diseases of the digestive system» and local routine practice [6-10].

Due to the non-interventional study design it's not possible to appoint exact times for the study visits, although it is expected that the period of observation will be approximately 12 months. The frequency of the visits will be assigned by each physician according to their routine practice. It is anticipated that the patients will visit their physician 2 times after enrolment into the study, i.e. approximately every 6 months (± 30 days). Information for the study will be collected from 3 visits:

- Visit 1 (Baseline visit, V1) – study enrolment and retrospective data collection
- Visit 2 (Observational visit, V2) – 6 months (+/- 2 weeks) after study enrolment.
- Visit 3 (Final observational visit, V3) – 12 months (+/- 2 weeks) after study enrolment.

The table below shows the data that can be recorded in the eCRF at each of these visits.

Scheme 1. The observational study schematic



10.5 Premature Termination or Suspension of Study or Investigational Site

The study will be completed as planned unless when temporary suspension or early termination required.

The Sponsor has the right to terminate the study providing a preliminary notification to investigators and hospitals. The Sponsor has the right to unilaterally stop enrolment of patients and data collection at any time in the study by providing a preliminary written notification to investigators and hospitals with date of stop of enrolment. The Sponsor should ensure that notification about premature termination or suspension of the study is submitted to the concerned authorities, IEC and LEC/IRB (if applicable).

The investigator has the right to stop recruitment at any time with serving a preliminary written notice to the Sponsor/responsible CRO.

In case of premature closure of the site/termination of the study, all documentation forms (except documentation that has to remain stored at site) must be returned to the Sponsor, even unused ones. Study material may be destroyed only with permission of the Sponsor.

11 The Study Population

The patients will be treated in accordance with local routine clinical practice. Patient eligibility is determined according to the following inclusion and exclusion criteria. Patients should be included in the study only once.

Approximately 2000 patients should be included into the study in accordance with the inclusion/exclusion criteria below.

11.1 Inclusion Criteria

Every eligible patient at participating investigational sites must meet the following criteria:

Inclusion criteria:

1. Male and female patients 18 years or older by the time of enrolment
2. Confirmed diagnosis of Crohn's disease or ulcerative colitis for at least 2 years prior to enrolment in the study.
3. The presence of a moderate to severe IBD flare at the time of enrolment or in patient anamnesis within 2 years before enrollment treated with steroids or/ and immunosuppressive agents or/ and biologic therapy. IBD flare(s) must be confirmed in the source documentation.
4. Current treatment with steroids or/ and immunosuppressive agents or/ and 5-ASA or/ and biologic therapy
5. Written informed consent, signed before the participation in the study begins.

11.2 Exclusion Criteria

Any patient who meets any of the following criteria will not be qualified for entry into the study:

1. Current or previous (within the last two years) indeterminate or not classified colitis.
2. Changing of IBD type in anamnesis (i.e. from UC to CD, etc) within the last two years.
3. Current, previous (within the last two years) or planned (for the next one year) participation in interventional clinical trial.
4. Presenting of mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
5. Any other condition, which on the opinion of the investigator may impact the patient's participation in the study.
6. Patient received previous treatment with biologic therapy/immunosuppressive agents for conditions other than IBD ever in their lifetime.

11.3 Justification for criteria inclusion and exclusion

The criteria are set to ensure a patient population that will enable the investigation of the set objectives.

As this is non-interventional observational study, we don't restrict exclusion criteria artificially. According to ethical rules, all patients must sign informed consent form before enrolling. Data erroneously collected from patient for which signed informed consent form is not available, will not be included in or will be deleted from the database.

Exclusion criteria were designed to prevent inclusion of patients with unconfirmed diagnosis, treated with investigational drugs or having mental disorders or a language barrier precluding adequate understanding or cooperation with the investigator and collection of the information required by the study protocol.

11.4 Patient selection and procedure for avoiding of selection bias

In order to reduce selection bias, each patient who is planned for study enrolment has to be documented in an anonymous patient log file (independent of prescribed treatment and signing of the Informed Consent Form) in a consecutive manner at each site.

Eligible patients must be enrolled consecutively into the study and documented in the case report form. Not eligible patient must be skipped. In case a patient is not eligible (e.g. no informed consent signed), the reason for non-eligibility must be documented in the patient log file.

11.5 Discontinuation/withdrawal of patients from the study

11.5.1 Criteria for Discontinuation or Withdrawal of a patient

Patients may be discontinued from the study at any time, based on investigator decision. Specific reasons for discontinuing a patient from the study are:

1. Voluntary withdrawal of informed consent in patient's request or at the request of patient's legally acceptable representative.

The patient (or patient's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

2. Development of exclusion criteria during the study.
3. Adverse Events (AE)/ Serious Adverse Events (SAE), including Patient's death

The patient has experienced an AE or SAE that requires early termination because patient is unwilling to continue because of the AE or SAE, or continuation of patients' visit to the clinic is impossible or any other occurrence which can be happened.

4. Protocol deviations and incorrect enrolment of the patient. The investigator and the sponsor will decide whether there is a deviation from the protocol.
5. Lost for observation within the framework of the study. The patient did not return to the clinic and attempts to contact the patient were unsuccessful.
6. Study termination. Sponsor decision or regulatory authorities' requirement about cessation of the study.
7. Other (specify)

If the patient is lost for observation within the study length and it is impossible to conduct the final visit; the investigator must do its best to get in touch with the patients for getting full information and clarifying the reasons. The attempts to contact patient should be documented.

Details for the premature termination of the study/sites as a whole are provided in section 10.5 (Premature termination or Suspension of Study or Investigational Site).

11.5.2 Replacement

Patients will not be replaced after drop out.

11.5.3 Procedures for Discontinuation or Withdrawal of a patient

There are no special procedures of discontinuation of patients. The investigator may terminate a patient's study participation at any time during the study when the patient meets the study termination criteria described above in Section 11.5.1. In addition, patient/legal representative may discontinue participation in the study without giving a reason at any time during the study.

In all cases, the reason for withdrawal must be recorded in the eCRF and in the patient's medical records. The patients who prematurely withdrew from the study are not replaced with new ones, and their data will be included into the final analysis. In case if investigator loses contact with the patient during the study observation, the investigator may contact with the patient directly or through the other health care professionals who observe this patient in routine practice. In that case part of eCRF "End of observation" can be filled in basing on data received via e-mails/calls.

12 Data collection

12.1 Data source

Data collection should be started only after Informed Consent Form is signed by the investigator and patient. A unique patient identification number (patient number) will be assigned to each patient at the time that informed consent is obtained; this patient number will be used throughout the study. Source data will include medical records or other sources of information (e.g. laboratory tests forms, validated copies of medical summaries given by other specialists etc.).

12.2 Tabulated overview of data collection

The documentation of study data will be reported by investigators via electronic case report form (eCRF).

Assessment / Procedure	Retrospective data collection*	Baseline visit (V1, Day 1)	Observational visit (V2, Month 6)	Final visit (V3, Month12)
Informed consent		X		
Patients' eligibility assessment: Inclusion/exclusion criteria		X		
Date of visit		X	X	X
Demographics data		X		
Disability		X		
Physical examination		X	X	X
Medical history / Concurrent medical conditions	X	X		
History of IBD	X	X		
IBD family history		X		
IBD assessment	X	X	X	X
Disease activity data		X	X	X
IBD status		X	X	X
Laboratory and instrumental evaluation of IBD **	X	X	X	X
IBD treatment	X	X	X	X
Healthcare resources utilization	X	X	X	X
Concomitant treatment		X	X	X
Physician Survey		X		X
Adverse events			X	X

* Retrospective data within two years before of patient enrolment in the study will be collected at Visit 1 after the signing of the informed consent form

**All examinations (laboratory tests and instrumental exams) are done in accordance with clinical routine practice and physician's decision. All examinations results should be registered in electronic CRF only if they are done in routine practice.

12.3 Data collected on the Baseline visit (V1), including collection of Retrospective data within two years before of patient enrolment in the study

The baseline visit takes place at the physician's office. Data to be collected:

- Date of Informed consent form signing (day, month, year);
- Inclusion/exclusion criteria;
- Date of visit (day, month, year);
- Demographics data (gender, date of birth, ethnicity, region of residence, smoking status, employment status (employed, unemployed, retired, student, other));
- Disability:
  - Disability group
  - Cause of disability
  - Year of disability
- Physical examination: height (cm) and weight (kg), bodymass index calculation;
- Medical history/Concurrent medical conditions (disease, date of diagnosis, resolution date);
- History of inflammatory bowel disease (IBD):
  - Type of inflammatory bowel disease (ulcerative colitis (UC) or Crohn's disease (CD)),
  - Date of IBD diagnosis,
  - Date of IBD symptoms onset,
  - Availability of observation in the current investigational site within previous 2 years
- IBD family history (degree of relationship);
- Clinical course of IBD (acute, chronic continuous, chronic recurrent);
- IBD assessment for the last 2 years and at the time of the baseline visit:
  - Disease extent according to the following Montreal Classification categories;
  - Systemic (extra intestinal) IBD manifestations;
  - IBD complications;
  - Vaccination in accordance with IBD treatment guidelines.
- Disease activity data at baseline visit will consist of specified signs and symptoms depending on the disease type:
  - CD: abdominal pain severity, number of liquid stools per day, presence of an abdominal mass, endoscopic findings (if done), documented presence of CD

complications, and Harvey Bradshaw Index or other documented disease activity scales (if applicable).

- UC: frequency of stools/day, rectal bleeding, endoscopic findings (if done), physician global assessment of disease severity, and Mayo scores or other documented disease activity scales (if applicable).

- IBD status at baseline visit:
  - IBD status as judged by investigator (remission, incomplete remission, flare, others), nature of remission at the time of examination;
  - IBD flare(s);
- Laboratory and instrumental evaluation of IBD for the last 2 years and at the time of the baseline visit (if done within routine practice) - for details please section 12.8;
- IBD treatment:
  - IBD treatment for the last 2 years and at the time of the baseline visit;
  - IBD surgical treatment for the last 2 years and at the time of the baseline visit;
- Healthcare resources utilization for the last 2 years and at the time of the baseline visit;
- Concomitant treatment.

12.4 Data collected at the Observational visit (V2) and Final Visit (V3)

Data to be collected directly on Observational visit (V2) and Final visit (V3):

- Date of visit (day, month, year)
- Type of visit: visit to physician office or distant contact
- Physical examination: weight (kg), body mass index calculation;
- IBD assessment at the time of the visit:
  - Disease extent according to the following Montreal Classification categories;
- Disease activity data at the visit will consist of specified signs and symptoms depending on the disease type:
  - CD: abdominal pain severity, number of liquid stools per day, presence of an abdominal mass, endoscopic findings (if done), documented presence of CD complications, and Harvey Bradshaw Index or other documented disease activity scales (if applicable).
  - UC: frequency of stools/day, rectal bleeding, endoscopic findings (if done), physician global assessment of disease severity, and Mayo scores or other documented disease activity scales (if applicable).
- IBD status (with current/last available data by the date of the visit):

- IBD status as judged by investigator (remission, incomplete remission, flare, others), nature of remission at the time of examination;
- IBD flare(s);
- Systemic (extra intestinal) IBD manifestations;
- IBD complications;
- Vaccination in accordance with IBD treatment guidelines.

- Laboratory and instrumental evaluation of IBD (if done within routine practice) - for details please section 12.8;
- IBD treatment;
- IBD surgical treatment;
- Healthcare resources utilization;
- Concomitant treatment
- Adverse events and adverse drug reactions (seriousness, severity, causality, start and stop dates, action, frequency, outcomes):
  - adverse drug reactions on IBD treatments,
  - adverse events on Entivyo® (Vedolizumab) treatment,
  - serious adverse events on IBD treatments (including Entivyo® (Vedolizumab) treatment).

All adverse events and adverse drug reactions must be documented on the Adverse Report Form which is appended to the Case Report Form.

12.5 Data collected at the End of observation

The end of observation in this study should be documented for all patients who passed the Baseline visit.

The following data on the eCRF titled "End of Observation" should be documented:

- Date of the last contact,
- Type of the last contact,
- Prematurely discontinuation of study visits (data collection) – yes/no,
- Reason(s) for discontinuation of prematurely data collection (if applicable).

12.6 Treatments to be documented in the study

12.6.1 IBD treatment

Due to non-interventional design of the study, the decision about particular IBD treatment strategy to the patient is taken by treating physician. All IBD medications are not provided by Sponsor.

Following medications for IBD treatment should be registered in eCRF; 5-ASA, immunosuppressive agents (including azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), cyclosporine A), corticosteroids and biologics.

The following data should be documented for steroids:

- INN name;
- release form;
- Route of administration
- Indication
- start date;
- initial and maximum daily dose;
- funding source;
- dose, if continued / end date and the reason for modification/ discontinuation, if discontinued.

The following data should be documented for 5-ASA, immunosuppressive agents:

- INN name;
- release form;
- Route of administration
- Indication start date;
- daily dose;
- funding source;
- continued / end date and the reason for modification/discontinuation.

The following data should be documented for biologics:

- trade and INN name;
- Indication start date;
- treatment regimen (induction or supportive care);
- dosage regimen;
- Route of administration
- funding source;
- continued / end date and the reason for modification/discontinuation.

If a physician takes a decision to change something from the above it must be documented in the eCRF.

12.6.2 Concomitant medication

Concomitant medication is any drug given in addition to the IBD treatment. These drugs may be prescribed by a physician or obtained by the patient over the counter.

It is not planned to collect full data about concomitant medication in this study. In present study only concomitant medication clinically relevant to the opinion of investigator are collected. Areas of Takeda's interest are:

- Therapy of tuberculosis (including prevention of tuberculosis),
- IBD extra intestinal manifestations (EIMs) therapy.

The information about concomitant medication can be received both on base of medical records and on questions to patients (according to routine practice). During the visits the information about changes in the concomitant therapy is recorded. At each study visit, patients will be asked whether they have taken any medication other than medication for IBD treatment used from signing of informed consent through the end of the study.

For every drug there will be documented INN, trade name, dosage regimen (single and total daily dose), duration of treatment (start and stop dates) and indication, frequency, route of administration.

12.7 Laboratory and instrumental examinations to be documented in the study

All examinations (physical examination and vital signs, laboratory tests and other exams) will be performed in accordance with common clinical routine practice, routine practice of a particular medical institution. All examinations are solely based on the physician's decision about strategy of diagnostics and treatment.

The following laboratory and instrumental examinations are planned to collect in the study:

- Laboratory tests results
  - Biomarkers: CRP, faecal calprotectin
  - Immunological tests: TB diagnostic test
- Endoscopic examination/ biopsy of GI tract
- X-ray of GI tract and lungs
- MRI/CT examination related to IBD
- Ultrasound examination related to IBD

All laboratory and instrumental examinations are collected during all period of data collection: retrospectively, at Baseline visit, through 1 year of prospective observation.

12.8 Documentation of Medical history and Concurrent Medical Conditions.

Medical history is history of diseases indicated before signing of the Informed Consent Form.

Concurrent medical conditions are those significant (ongoing conditions or diseases that are present at signing of informed consent). Concurrent medical conditions may include not limited to tuberculosis, cardiovascular disorders, diabetes, chronic pulmonary artery disease, chronic kidney disease. The condition (i.e., diagnosis) should be registered in eCRF.

Time of medical event/disease	How it should be documented
Before ICF signed	Medical history
At the moment of ICF signing	Concurrent medical conditions
After ICF signing	Adverse Events

12.9 Healthcare resources utilization (HCRU)

Resource utilization will be captured from the patients' medical records:

HCRU will be calculated for hospitalizations related to IBD complications, IBD-related surgeries as available in the medical record and captured in the eCRF.

12.10 Physician Survey

The survey assessed the duration and nature of clinicians' IBD clinical practice, and familiarity with a treat-to-target approach to UC/CD management and its perceived relevance will be explored. Clinicians' perceptions of their current use of objective measures of disease activity to guide management, optimal treatment targets in UC/CD, and the proportion of their patients in which these targets are currently achieved were evaluated.

13 Safety Reporting

13.1 Definitions

13.1.1 Adverse Event and Adverse Drug Reactions

An **Adverse Event (AE)** is defined as any any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease, occurring after exposure to the drug, whether or not considered related to the medicinal product.

An **Adverse drug reaction (ADR)** is an unintentional, unfavorable reaction of the human body associated with the use of a medicinal (investigational) product and involving at least a possible relationship with the use of the suspected medicinal (investigational) product

13.1.2 Additional Points to Consider for AEs/ADRs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered AEs/ADRs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs/ADRs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s)/ADRs.

Laboratory values:

- Changes in laboratory values are only considered to be AEs/ADRs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE/ADRs.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs/ADRs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE/ADRs (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").
- If a patient has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a AE/ADRs if the episodes become more frequent,

serious or severe in nature, that is, investigators should ensure that the AE/ADR term recorded captures the change in the condition from Baseline (e.g. "worsening of…").

- If a patient has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE/ADR if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of AEs/ADRs:

- If the patient experiences a worsening or complication of an AE/ADR after any change in study medication, the worsening or complication should be recorded as a new AE/ADR. Investigators should ensure that the AE/ADR term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs/ADRs:

- If the patient experiences changes in severity of AE/ADRs, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs/ADRs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE/ADRs. Complications resulting from any planned surgery should be reported as AEs/ADRs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the patient's medical condition should not be recorded as AEs/ADRs. Complications resulting from an elective surgery should be reported as AEs/ADRs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE/ADR. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

13.1.3 Serious AEs

A serious AE (SAE) is any AE which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

A serious AE are defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.

   The term "life threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an OTHER IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the patient to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction.

13.1.4 Severity AEs/ADRs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the patient.

Moderate: The event causes the patient discomfort and interrupts the patient's usual activities.

Severe: The event causes considerable interference with the patient's usual activities.

13.1.5 Causality of AEs/ADRs

The relationship of each AE/ADR to study medication will be assessed using the following categories:

Related: An AE/ADR that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE/ADR that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

13.1.6 Start and Stop Dates

The start date of the AE/ADR is the date that the first signs/symptoms were noted by the patient and/or physician.

The stop date of the AE/ADR is the date at which the patient recovered, the event resolved but with sequel or the patient died. If AE/ADR is ongoing at the moment of end of observation, it should be indicated in the eCRF.

13.1.7 Frequency

AEs/ADRs (e.g., vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are *continuous.*

13.1.8 Action Concerning Study Medication

- *Drug withdrawn* – a study medication is stopped due to the particular AE/ADR.
- *Dose reduced* - the dose was reduced due to the particular AE/ADR.
- *Dose Increased* – the dose was increased due to the particular AE/ADR
- *Dose not changed* – the particular AE/ADR did not require stopping a study medication.

- *Dose Interrupted* – the dose was interrupted due to the particular AE/ADR
- *Unknown* – only to be used if it has not been possible to determine what action has been taken.

13.1.9 Outcomes of AEs/ADRs

- *Fatal*: The patient died due to the AE/ADR. If the patient died due to other circumstances than the AE/ADR the outcome should be stated as 'Not recovered' or 'Recovering'. The date of death will be recorded.
- *Recovered/Resolved*: The patient has fully recovered from the event or the condition has returned to the level observed at baseline
- *Recovering/Resolving*: The event is improving but the patient is still not fully recovered
- *Not Recovered/Not Resolved*: The event is ongoing at the time of reporting and the patient has still not recovered
- *Recovered with Sequelae/Resolved with Sequelae*: As a result of the event, the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed).
- *Unknown*: If Outcome is not known or not reported.

13.2 Reporting of Adverse Events and Adverse Drug Reactions

13.2.1. Legislation for Pharmacovigilance

Applicable legal base Pharmacovigilance for the Russian Federation is following:

- Federal law №61 of 12 April 2010 "On the Circulation of Pharmaceuticals"
- Good Pharmacovigilance Practice of Eurasian Economic Union" (came into force May 06, 2017).
- Roszdravnadzor order #1071 "On Approval of the Pharmacovigilance Procedure" (came into force April 01, 2017).
- Order of the Ministry of health care and social development of 26 August 2010 N757n "On approval of the procedure for drug safety monitoring, reporting of side effects, serious adverse drug reactions, unexpected adverse drug reactions"
- RF Government statement of 30.06.2004 #323 «On approval of the Federal Service on Surveillance in Healthcare»
- RF Government statement of 15.10.2012 №1043 «On approval of the Federal State Supervision in medicine circulation»

Applicable legal base Pharmacovigilance for the Republic of Kazakhstan is following:

- The Code of Republic of Kazakhstan on people's health and the health system (with amendments and additions from 19.05.2015)

- Order of the Minister of Health of the Republic of Kazakhstan dated November 19, 2009 № 744 On approval of rules of clinical trials and (or) pharmacological tests of medicines, medical devices and medical equipment (with amendments from September 28, 2012)

- Order No. 421 of the Health and Social Development Minister of the Republic of Kazakhstan as of 29 May 2015 On Approval of the Rules for Medicines Pharmacovigilance and Monitoring of Adverse Reactions of the Medicines, Medical devices and Medical Equipment Order #9 on amendments to the Order #735 of the Minister of Health of the Republic of Kazakhstan from 18 November, 2009 On approval of the rules for state registration, renewal and amendments into the registration dossier of the Medicines, Medical devices and Medical Equipment

- Good Pharmacovigilance Practice of Eurasian Economic Union" (came into force May 06, 2017).

Applicable legal base Pharmacovigilance for the Republic of Belarus is following:

- Law of the Republic of Belarus № 161-3 "On Medicines" dated 20.07.2006, ed. №386-3 dated 29.06.2016

- Technical Code of Practice 564-2015(33050) "Good Pharmacovigilance Practice"

- Good Pharmacovigilance Practice of Eurasian Economic Union" (came into force May 06, 2017).

13.2.2. AE Reporting Form

All AEs and ADRs will be documented in the special page of the eCRF – "AE reporting form". The following information will be documented for each event:

- event term,
- start and stop date/ ongoing,
- severity,
- Investigator's opinion of the causal relationship between the event and administration of IBD medication(s) (related or not related),
- IBD medication,
- action concerning medication,
- outcome of AE,
- seriousness.

13.2.3. Collection and reporting of AEs and ADRs

The following safety data should be reported by the investigator to the responsible CRO:

– adverse drug reactions on IBD treatments,

– adverse events on Entivyo® (vedolizimab) treatment,

– serious adverse events on IBD treatments (including Entivyo® (vedolizumab) treatment).

Start of AEs and ADRs collection: AEs/ADRs must be collected from the date after ICF signing. Routine collection of AEs/ADRs will continue until Final visit (Visit 3).

A physician must report all reportable AEs and ARDs on the special "AE reporting form" provided by the Sponsor. The physician should record only one AE per 1 "AE reporting form". The physician has to record the diagnosis if available. If no diagnosis is available, the physician should record each sign and symptom as separate reports.

13.2.4. Collection and reporting of SAE and pregnancies

The investigator must report all reportable SAEs and pregnancies to the CRO.

If information is not available at the time of the first report becomes available at a later date or upon on the Sponsor's request, the investigator should complete an additional SAE form and provide it by one of mentioned above way **immediately within 24 hours** of receipt. In any case all SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Start of SAEs collection: SAEs must be collected from the date after ICF signing. Routine collection of SAEs will continue until Final visit (Visit 3).

The CRO must report all SAEs and pregnancies which occur during patient's treatment by Entyvio to the Sponsor **immediately within 24 hours** of receipt. All other SAEs and pregnancies are included in the study data base without direct reporting to the study Sponsor.

13.2.5. Safety reporting to Investigators, IECs and Regulatory Authorities

All safety-related data on study patient collected in the study database will be summarised in the Interim Analysis Study Reports and in the Non-Interventional Study Report. All Entyvio SAEs and pregnancy cases will be reported by CRO directly to Takeda within 24 hours.

The Sponsor is responsible for reporting all Entyvio serious adverse drug reactions (SADRs) to the Federal Service on Surveillance in Healthcare not later than 15 calendar days from the day when relevant information becomes known to the Sponsor or CRO.

Periodic Safety Update Report (PSUR) contains drug safety information obtained from spontaneous reports, literature and in clinical trials for a certain reporting period. If the PSUR submission time terms and frequencies for particular drugs are not established by Roszdravnadzor, PSUR submission time terms and frequency shall be calculated from the first drug's worldwide registration date (International Birth Date) and are as follows:

– Every 6 months during first 2 years from International Birth Date;
– Annually during the following 2 years;

– Once in three years – thereafter.

Specialized safety reporting in the Republic Kazakhstan:

The Investigator informs the Authorized organization, Ethics Committee and the Sponsor/responsible CRO about all ADRs_not later than 15 calendar days from the day when relevant information becomes known.

Periodic Safety Update Report (PSUR) contains drug safety information obtained from spontaneous reports, literature and in clinical trials for a certain reporting period.

The marketing authorization holder, within the marketing authorization validity period, shall provide the authorized organization with the Periodic Safety Report from the date of registration in the Republic of Kazakhstan in accordance with the following standard periodicity:

- once every six months within two years after registration;
- annually - within the next three years;
- then - every three years or after receiving a report from the central office (if applicable);
- in future - upon subsequent medicine re-registration - once in five years;
- immediately at the authorized organization's request.

14 Data Quality Control and Assurance

14.1. Quality Control

14.1.1. Training of investigators

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study, study procedures, safety reporting, ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the case report form. All outcome variables and covariates will be recorded in a standardized case report form.

14.1.2. Study Quality Oversight

The data quality will be assured by using the following methods of quality review:

- telephone interview,

- monitoring in the study sites (the monitoring will consist of two parts: on-site interview and verification of the compliance of the data presented in the eCRF with the data of the primary documentation - source data verification (SDV)).

Due to non-interventional study design source documents will be partly reviewed for verification of data recorded on the eCRF. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the Sponsor or its designee (CRO) and by the RA, IEC or LEC/IRB.

All aspects of the study and its documentation can be patient to review by the Sponsor or responsible CRO, including but not limited to the Investigator's Site File, patient medical records, informed consent documentation and review of eCRF and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process. The investigator and institution guarantee access to source documents by the Sponsor or responsible CRO and by the RA, IEC or LEC/IRB.

Due to the non-interventional study design it can be able to conduct quality review only on subset of investigational sites and case report forms. Exact extent of quality reviews will be defined in the Clinical Monitoring Plan. The detailed description of the quality review will be presented in the Quality Control Plan, the Clinical Monitoring Plan, the Data Management Plan (DMP) and Statistical Analysis Plan.

The investigational sites where telephone interview or monitoring visit will take place will be determined randomly. Due to long overall duration of the study several waves of quality reviews will be performed.

14.1.3. Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. In accordance with NIS definition all examinations and other data should be registered in the CRF only if they are done in routine practice.

Should other unexpected circumstances arise that will require deviation from protocol-specified procedures and data collections rules, the investigator should consult with the Sponsor, responsible CRO or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, or confound interpretation of primary study assessment.

14.1.4. Data checks and data queries

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the sponsor and responsible CRO and will be answered by investigators.

Corrections to eCRF are recorded in an audit trail that captures the initial information, changes, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

14.1.5. Quality Assurance Audits

The Quality Assurance (QA) unit or out-sourced by the Sponsor agency or appointed Qualified person may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, applicable legislation and that collected data is correct and complete.

14.2 Inspection by IEC or Competent Authority

Representatives from IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the investigator must immediately contact to the Sponsor and must make the records available as requested. The Inspector must be reminded up front that consent to access to personal data has been obtained from the participants in this study.

14.3 Data Handling and Record Keeping

14.3.1. Data Management Plan

Data handling will be carried out according to a Data Management Plan and Data Validation Plan. Data Management Plan must be written and approved before the design of the study database is finalised. Responsible CRO will provide all the data management service including data transferring, data clarification and quality control of the process. The data management provider should approve all data formats before the data collection tools are made available to the sites.

14.3.2. Data privacy

The Sponsor and responsible CRO affirm and uphold the principle of the patient's right to protection against invasion of privacy. The personal data of the NIS participants will be kept and processed with observance of the provisions of the RF federal law No. 152 "On personal data". Throughout this study, a patient's source data will only be linked to the study database or documentation via a unique identification number (for details, please, see Sections 8.5, 8.6., 8.7., 8.9).

If the written informed consent of a patient is known not to be available in spite of it being required, data for this patient is not entered into or is deleted from the database.

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

The patients will be identified in the database only by patient identification code (for details, please, see the section 8.7)

14.3.3. Case Report Form (CRF)

Electronic CRF (eCRF) will be used in the study. Completed eCRFs are required for each patient who signs an ICF.

The study database will be set up and maintained by responsible CRO. The responsible CRO will supply investigators with access to eCRF. The CRO will make arrangements to train investigators in the use of the eCRF. Patient data will be entered directly into the database by authorized investigators. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. eCRFs must be completed in Russian.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by CRO, Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the initial information, changes, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The investigators must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The Sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

14.3.4. Coding of AEs and concomitant medications

Adverse events, medical history and concurrent medical conditions are coded with MedDRA dictionary (Medical Dictionary for Regulatory Activities). Concomitant Medications are coded with Anatomical Therapeutic Chemical Dictionary (ATC) current version.

14.3.5. Record retention

The investigator agrees to keep the records stipulated in Section 12.3.3 and those documents that include (but are not limited to) the study-specific documents, the Patient Identification list, medical records, all original signed and dated informed consent forms to enable evaluations or audits from regulatory authorities, the sponsor or responsible CRO. The study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Study agreement. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

15 Statistical Methods and Determination of Sample Size

A statistical analysis plan (SAP) will be prepared and finalized prior to the first interim analysis . 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 Non-interventional Study Report.

15.1 Patient Population

Due to observational nature of this study patients will not be excluded from analysis based on their performance and/or data availability. All obtained data will be summarised after procedures of data cleaning and verification. All planned analyses (including descriptive analyses and study listings) will be performed for Full Analysis Set of data.

The following patient's populations will be included into statistical analysis:

- *All Patients Enrolled population*: All patients who signed informed consent to enter the study
- *Safety population*: Patients who have taken at least one dose of any IBD medicine after enrolling in the study (Baseline visit)

15.2 The study data and Statistical Analysis methods

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, i.e. all data listed in section 12.

The primary and secondary outcomes of the study are presented in section 6.2.

15.2.1. Summary of study data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, 25 percentile, 75 percentile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. For variables marked "binary" exact (Clopper-Pearson) 95% confidence intervals will be calculated where appropriate. For categorical variables with more than 2 categories 95% confidence intervals will be calculated using Goodman`s method [33].

In general, all data will be listed, sorted by site and patient, and when appropriate by visit number within patient. All summary tables will be structured with a column for each treatment pattern in the pre-defined order and will be annotated with the total population size relevant to that table/treatment pattern, including any missing observations."

Patient Disposition

Data regarding how many patients reached the various stages of the study, how many dropped out, discontinued the treatment and for what reasons (death, ADRs, treatment failure, withdrew consent, lost to follow-up) will be presented for each subgroup and for study in bulk. Standard CONSORT diagram describing study patient flow will be provided.

15.2.2. Statistical analysis methods

All data from patients enrolled in this study will be analyzed. Information on CD and UC patients will be presented separately. Also, analysis will be performed separately by therapy subgroups (patients receiving non-biological therapy and patients receiving biological therapy). Due to complexity of treatment regimen a manual review can be used to define treatment subgroup for each patient.

A descriptive analysis approach will be used to analyze the data and the study outcomes for the different study subgroups.

Descriptive statistics will include summary tables (n, mean, median, standard deviation, minimum and maximum, lower and upper quartile for continuous variables and n, frequency and percentage for categorical values). Proportion will be assessed together with 95% confidence interval, if applicable. Cross tabulations will be used to present study outcomes by the corresponding subgroups, when required. Time to event will be described with Kaplan-Meier estimates. Median time to event will be presented together with the lower and upper quartiles. Baseline and retrospective data will be used to describe the patient population and will be tabulated separately.

The number and percentage of patients who have reached remission while in the study will be presented. Selected outcomes will be reported separately for those who have reached remission and those who haven't.

15.2.3. Analysis of Safety Data

All safety data will be analysed on the safety population. Prior to analysis, adverse drug reactions will be coded using MedDRA.

Incidence and characteristic of adverse drug reactions will be described and presented in summary tables using absolute frequencies and percentages as well as 95% confidence intervals;

Evaluation of AEs, including the AEs, will consist of the determination of total number of AEs, total number of patients with AEs and the number of AEs requiring discontinuation of the study treatment. The incidence and severity of all AEs will be summarized by body system. Treatment discontinuation due to AEs will be tabulated.

AEs reported in the study as well as AEs reported directly to authorities and to Takeda International Drug Safety according to section 11.2 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).

15.2.4. Potential study biases

The study limitations are those inherent to uncontrolled observational studies. Taking into account observational and uncontrolled nature of the study, fully evaluating of non-biological /biological treatment effectiveness will not be available. However, data regarding in real-life practice will be gathered and analyzed. The inclusion criteria are those that used when administering non-biological /biological treatment in practice and therefore, the same criteria as those that would have been used if we had performed a similar prospective study. This type of experimental design should prevent selection bias that could occur when patient enrollment is related to the development of the outcome. In prospective observational study like this attrition bias is possible, however, in case of early leaving study last data will be gathered and effectiveness will be estimated, these cases will not be excluded from effectiveness analysis.

Details of the statistical analyses will be presented in the Statistical Analysis Plan.

15.2.5. Data handling

Missing data and invalid data

Missing data will not be restored. No procedures for missing data pattern assessment and/or imputation are planned.

Multiplicity

Because of descriptive nature of the study no multiplicity correction is applicable.

15.3 Interim Analyses

One interim data analysis is planned in this study – in 2019. The final statistical analysis will be performed after the end of the study and database lock.

15.4 Determination of Sample Size

The primary objective of this study is to obtain the accurate and comprehensive information regarding the treatment regimens used in patients with moderate to severe UC and CD flare within routine clinical practice in Russia, Belarus and Kazakhstan. For this purpose, sample size should be large enough to contain essential number of patients with different therapy options.

One of the key secondary objectives is to assess the percentage of Ulcerative Colitis (UC) and Crohn's Disease (CD) patients with at least one episode of failure of non-biological therapy with immunosuppressive agents or biological therapy registered within 12 months from the beginning of moderate to severe IBD flare. Based on literature data, up to 20-40% of IBD patients

experience failure of TNF antagonist therapy initially, and in 10-20% of patients per year loss of response is observed.

Assuming the percent of patients receiving biological therapy in the study population is 40%, about 40% proportion of CD patients [5, 6] and that 40-50% of the patients on biological therapy will have at least one episode of treatment failure during 12 months, enrolment of 2000 patients totally will be sufficient to estimate the proportion of patients on biological therapy with treatment failure during the 12 months of observation with acceptable precision in both UC and CD subgroups (±5.8% for the smaller subgroup of CD patients and the assumed failure rate of 50%). The table below shows 95% confidence intervals for the estimated proportions of 40%, 50% and different sample size values. For other, more prevalent subgroups (CD patients on non-biological therapy, UC patients on each type of therapy) the proposed sample size will also allow to estimate proportion of patients with treatment failure with same or higher precision.

The total number of patients to be enrolled	The number of CD patients on biotherapy*	The number of CD patients in the analysis assuming 10% drop-out	Assumed failure rate of biotherapy**	
			40%	50%
2000	320	288	34.3-45.7%	44.2-55.8%
2500	400	360	34.9-45.1%	44.8-55.2%
3000	480	432	35.4-44.6%	45.3-54.7%
3500	560	504	35.7-44.3%	45.6-54.4%
4000	640	576	36.0-44.0%	45.9-54.1%
4500	720	648	36.2-43.8%	46.2-53.8%
5000	800	720	36.4-43.6%	46.3-53.7%

* Assuming the percent of patients receiving biotherapy is 40% among the study population. The precision (95% CI) is shown for the smaller subgroup of CD patients (approximately 40%).

** 95% confidence intervals are shown.

16 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to the Sponsor for distribution. The Final Non-Interventional Study Report should be available within one year (12 months) from the date of the last data point collection, and the participating sites should be informed about the results when the report is finalised. Final Non-interventional Study Report should be provided to the IEC/RA (if applicable).

17 Publications

17.1 Publication and Disclosure

During the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by investigators) without the consent of investigators. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study contracts. In the event of any discrepancy between the protocol and the study contracts, the study contracts will prevail.

The Sponsor aims to have the results of this study published and acknowledges the right of the participating sites to publish results from this study. The Sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company, to affiliates and partners

17.2 Study Registration

The sponsor aims to have the results of this study published in time specified.

In order to ensure that information on the study reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the sponsor will, at a minimum register all clinical trials and observational studies conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before study initiation. The sponsor contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

18 Archiving of Study Documentation

During the course of the study the investigator must as a minimum file, the protocol, all protocolamendments, example of the ICF, Patient identification log, the signed informed consents forms, the progress reports in the Study Site File. After final database lock the investigator must as a minimum store the Patient identification log and the signed Informed Consent Forms on site for 5 years or during time reflected in the respective country legislation whatever is stricter. The investigator 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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20 Appendices

Appendix 1. Montreal classification of extent of ulcerative colitis

Extent		**Anatomy**
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Appendix 2. Montreal classification for Crohn's disease

Age at diagnosis	A1 below 16 y
	A2 between 17 and 40 y
	A3 above 40 y
Location	L1 ileal
	L2 colonic
	L3 ileocolonic
	L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating
	B2 stricturing
	B3 penetrating
	p perianal disease modifier†

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.

† "p" is added to B1–B3 when concomitant perianal disease is present.

Appendix 3. Mayo score

The full Mayo Score evaluates ulcerative colitis stage, based on four parameters: stool frequency, rectal bleeding, endoscopic evaluation and Physician's global assessment (1,2). Each parameter of the score ranges from zero (normal or inactive disease) to 3 (severe activity). The following table indicates, for each parameter, the input values with their respective scores.

Parameter	Clinical evaluation (single choice)	Score
1. Stool frequency (per day)	• normal number of stools • 1-2 more than normal • 3-4 more than normal • ≥ 5 more than normal	0 1 2 3
2. Rectal bleeding (indicate the most severe bleeding of the day)	• none • streaks of blood with stool in in less than half of the cases • obvious blood with stools in most cases • blood alone passes	0 1 2 3
3. Endoscopic findings	• normal mucosa or inactive disease • mild activity (erythema, decreased vascular pattern, mild friability) • moderate activity (marked erythema, lack of vascular pattern, friability, erosions) • severe activity (spontaneous bleeding, large ulcerations)	0 1 2 3
4. Physician's global assessment	• normal • mild disease • moderate disease • severe disease	0 1 2 3

Calculation formula: sum of the scores of the four parameters.

Score	**Decoding**
0 - 2	Remission (provided that no *subscore* for each single parameter is greater than 1)
3 - 5	mild activity
6 - 10	moderate activity
> 10	severe activity

Partial Mayo Score uses the three non-invasive components of the full Mayo Score (stool frequency, rectal bleeding and Physician's global assessment). This excludes the score for the endoscopic findings, therefore the maximum score is reduced from 12 to 9 points (1,2). This simplified index maintains a good relationship with the full Mayo Score in identifying clinical response as perceived by patients (3).

Score	**Decoding**
<2	remission
2 - 4	mild activity
5 - 7	moderate activity
> 7	severe activity

Appendix 4. Harvey-Bradshaw index

Parameter	**Input and score**
1. Patient well-being (previous day)	0 = very well 1 = slightly below par 2 = poor 3 = very poor 4 = terrible
2. Abdominal pain (previous day)	0 = none 1 = mild 2 = moderate 3 = severe
3. Number of liquid or soft stools (previous day)	blank field possibility to insert an integer, from 1 to 25
4. Abdominal mass	0 = none 1 = dubious 2 = definite 3 = definite and tender
5. Complications	No (0 points) Yes (drop-down menu with multiple selection; each selected complication is counted with 1 point) • arthralgia • uveitis • erythema nodosum • aphthous ulcer • pyoderma gangrenosum • anal fissures • appearance of a new fistula • abscess

Calculation formula: sum of the scores of all 5 parameters.

Score	**Decoding**
<5	remission
5 - 7	mild activity
8 - 16	moderate activity
> 16	severe activity