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

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PI

Document information

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CONTENTS

1 HISTORY OF CHANGES

Version	Description of changes	Date
v0.1 draft	Not applicable, initial version of the document	06.06.2018
v0.2 draft	Clarification related to the definition of treatment patterns and conduct of interim analysis, safety data analysis	13.06.2018
v0.3 draft	Description of analysis of primary endpoint was extended with the list of planned treatment patterns for analysis, addition of Sankey diagrams for treatment state transitions, additional quantitative parameters to characterize treatment patterns were added (course duration, maximum dose, # of courses per patient), example tables and figures re-worked accordingly	29.05.2019
v0.4 draft	Changes made across the document to comply with the wording of all protocol amendments (including # 1 and # 2)	17.06.2019
v0.5 draft	Minor corrections throughout the document, T2T objective description enriched and moved to the end of section 8.1.3	27.06.2019
v1.0 final	T2T objective was removed (in the part that is analyzed separately using the investigator survey)	01.07.2019
V1.1 final	JAK inhibitors were added as treatment option, clarification was made regarding the analysis of data from subjects in inclusion/exclusion criteria violation	18.07.2019
V1.2 final	After an interim analysis of the data obtained different subgroups were added	30.12.2021

2 ABBREVIATIONS LIST

Abbreviation	Description
5-ASA	5-aminosalicylic acid
6-MP	6- mercaptopurine
AZA	Azathioprine
CD	Crohn's disease
CI	Confidence interval
CRAN	Comprehensive R Archive Network
FAS	Full analysis set
IBD	Inflammatory bowel disease
ICH	International conference for harmonization
JAK	Janus kinase
M	Arithmetic mean
Me	Median
MRAN	Microsoft R Application Network
MTX	methotrexate
n	Number of patients with at least one event
N	Total number of patients by group
T2T	Treat-to-target
UC	Ulcerative colitis

3 INTRODUCTION

This study is planned 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. The study will be conducted as non-interventional, international, multicenter study of real-life practice with the objectives listed in the section 4.2 of this plan.

This statistical analysis plan is developed according to the following documents:

- ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports E3. Step 4, 30 November 1995. https://database.ich.org/sites/default/files/E3_Guideline.pdf. Accessed 30 December 2021.
- ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1), 6 July 2012.

  https://database.ich.org/sites/default/files/E3_Q%26As_R1_Q%26As.pdf. Accessed 30 December 2021.
- ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9. Step 4, 5 February 1998.

  https://database.ich.org/sites/default/files/E9_Guideline.pdf. Accessed 30 December 2021.
- ICH Harmonised Guideline: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. E9 (R1), Final version, 20 November 2019.

  https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf. Accessed 30 December 2021.
- Final concept paper E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials, Endorsed by the ICH Steering Committee on 23 October 2014.

  https://database.ich.org/sites/default/files/E9-R1_EWG_Concept_Paper.pdf. Accessed 30 December 2021.
- Recommendation of the Board of the Eurasian Economic Commission dated November 3, 2020 N19 "On the Guidelines for the Application of the Principles of Biostatistics in Clinical Trials of Medicinal Products".

  https://docs.eaeunion.org/docs/ru-ru/01427633/err_06112020_19. Accessed 30 December 2021.

- Non-interventional study protocol IBD-5005 (MACS-2017-102279) version 4.0 dated 28-Oct-2019.

The purpose of this statistical analysis plan is a more detailed, compared to the section 15 of the protocol, description of the main principles of statistical analysis conduct as planned per protocol, description of methods of primary and secondary endpoint analysis as well as other data collected during the study.

This plan assumes the full compliance of planned and conducted analyses to the study protocol, including the study population (data sets) definitions, any applicable data transformation or compensation, required number of subjects, etc. All discrepancies compared to the study protocol should be explained, and a rationale should be provided.

4 STUDY GOALS AND OBJECTIVES

4.1 Study goal

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.

4.2 Study objectives

Primary objective:

- To characterize the treatment patterns associated with biologic 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;
- To 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 objectives:

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

- To describe disease activity parameters, quality of life indicators, clinical outcomes, and safety criteria in different subgroups of patients.

5 STUDY DESIGN

5.1 Design

The study is designed to be an international, combined retrospective and prospective, multicenter, non-interventional, observational study. This study is a 'non-interventional study' as defined in EU Clinical Trial Regulation No. 536/2014 and the guidelines for GVP . 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 inclusion and exclusion criteria 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 in patients' source documents. Retrospective design means that all patients' data that will be collected in the study are 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).

Study periods are defined on the following figure.

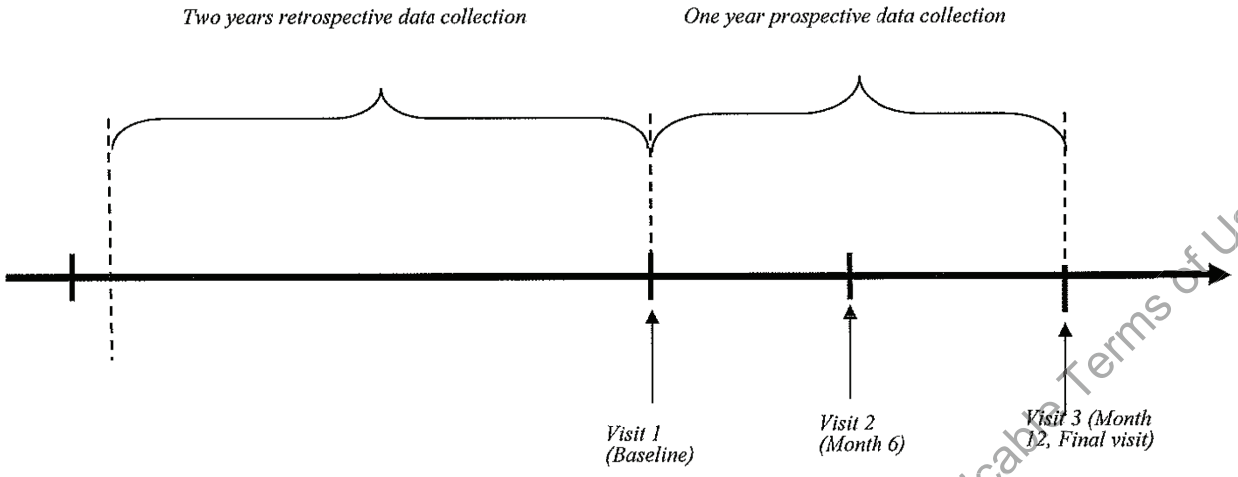

Figure 1. Observational study schematic

5.2 Randomization and blinding

Not applicable due to non-interventional nature of the study.

5.3 Study stages and procedures

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.

Tabulated overview of visits and procedures performed on these visits is provided in the following table.

Table 1 Tabulated overview of visits and procedures

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.

5.3.1 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), body mass 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);
- 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.

5.3.2 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);
- 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.

5.3.3 Collection of data on the continuous basis

All data described below should be collected through whole observational prospective 1-vear period of patients within the periods: Baseline visit -Visit 2, Visit 2 - Visit3 (independently of actual number of patient's visit to the clinic):

- IBD treatment;
- IBD surgical treatment (indications, types of surgeries, complications, presence of stoma, etc.);
- Results of diagnostic methods used (within the period since last visit);
- 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, o adverse events on Entivyo® (Vedolizumab) treatment,
  - serious adverse events on IBD treatments (including Entivyo® (Vedolizumab) treatment).

5.4 Study completion and withdrawal

Regardless of study completion status, the following information should be documented in CRF for each subject:

- Date of the last contact;
- Type of the last contact;
- Prematurely discontinuation of study visits (data collection) – yes/no:
  - If "Yes", reason(s) for discontinuation of prematurely data collection.

5.4.1 Completion of study per protocol

The patient is considered a completed if his period of observation since V1 (Baseline) was no less than 12 months (taking allowed visit windows into account).

5.4.2 Study withdrawal

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.

Patients will not be replaced after drop-out.

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 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 based on data received via e-mails/calls.

6 MAIN ASSESSMENTS

6.1 Endpoints (outcomes)

Primary endpoint (outcome): 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:

- trade and INN name;
- original medication or biosimilar medication;
- dosage regimen (dose, route and frequency);
- duration of each dose regimen;
- presence of treatment modifications/discontinuation;
- funding source;
- reason(s) for modification/discontinuation of IBD medicine treatment;

Secondary endpoints (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.

6.2 Methods and timelines for the assessment of efficacy endpoints

Retrospective (2 years before ICF signing) and prospective (1 year after ICF signing) collection of observational data from UC/CD patients.

7 SAFETY AND EXPLORATORY ASSESSMENTS

7.1 Safety endpoints (outcomes):

- 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).

7.2 Methods and timelines for the assessment of safety endpoints

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

7.3 Exploratory endpoints:

- 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).

7.4 Subgroup analysis:

Criteria for the treatment of inflammatory bowel diseases

1. Depending on the conditions of prescribing biological therapy:
    a. By the period of time from diagnosis to biological therapy prescription:
        - up to 2 years inclusive
        - from 2 to 5 years inclusive
        - more than 5 years
    b. By the number of courses of systemic corticosteroids in medical history before biological therapy prescription:
        - < 3 courses
        - ≥ 3 courses
2. Patients not assigned to biological therapy:
    a. By the period of time from diagnosis to biological therapy prescription:
        - up to 2 years inclusive
        - from 2 to 5 years inclusive
        - more than 5 years
    b. By the number of courses of systemic corticosteroids in medical history before biological therapy prescription:
        - < 3 courses
        - ≥ 3 courses

Subgroups of first-line biological therapy

1. Vedolizumab
    a. By the period of time from diagnosis to biological therapy prescription:
        - up to 2 years inclusive
        - from 2 to 5 years inclusive
        - more than 5 years
    b. By the number of courses of systemic corticosteroids in medical history before biological therapy prescription:
        - < 3 courses
        - ≥ 3 courses

c. Depending on disease activity at the moment of biological therapy prescription:

- Crohn's disease, the Harvey-Bradshaw index:
  - < 5 points
  - 5-16 points
  - >16 points
- Ulcerative colitis, the Partial Mayo Score:
  - 0 scores
  - 1-2 scores
  - 3–5 scores
  - ≥ 6 scores

2. Ustekinumab

a. By the period of time from diagnosis to biological therapy prescription:

- up to 2 years inclusive
- from 2 to 5 years inclusive
- more than 5 years

b. By the number of courses of systemic corticosteroids in medical history before biological therapy prescription:

- < 3 courses
- ≥ 3 courses

c. Depending on disease activity at the moment of biological therapy prescription:

- Crohn's disease, the Harvey-Bradshaw index:
  - < 5 points
  - 5-16 points
  - >16 points
- Ulcerative colitis, the Partial Mayo Score:
  - 0 scores
  - 1-2 scores
  - 3–5 scores
  - ≥ 6 scores

3. Anti-TNF-α
    a. By the period of time from diagnosis to biological therapy prescription:
        - up to 2 years inclusive
        - from 2 to 5 years inclusive
        - more than 5 years
    b. By the number of courses of systemic corticosteroids in medical history before biological therapy prescription:
        - < 3 courses
        - ≥ 3 courses
    c. Depending on disease activity at the moment of biological therapy prescription:
        - Crohn's disease, the Harvey-Bradshaw index:
            - < 5 points
            - 5-16 points
            - >16 points
        - Ulcerative colitis, the Partial Mayo Score:
            - 0 scores
            - 1-2 scores
            - 3–5 scores
            - ≥ 6 scores
4. Tofacitinib
    a. By the period of time from diagnosis to biological therapy prescription:
        - up to 2 years inclusive
        - from 2 to 5 years inclusive
        - more than 5 years
    b. By the number of courses of systemic corticosteroids in medical history before biological therapy prescription:
        - < 3 courses
        - ≥ 3 courses
    c. Depending on disease activity at the moment of biological therapy prescription:
        - Crohn's disease, the Harvey-Bradshaw index:

- < 5 points
- 5-16 points
- >16 points

- Ulcerative colitis, the Partial Mayo Score:
  - 0 scores
  - 1-2 scores
  - 3–5 scores
  - ≥ 6 scores

Subgroups depending on the use of drugs in the first- and second-line therapy

a. Ustekinumab in the first line, vedolizumab in the second line
b. Ustekinumab in the first line, anti-TNF-α in the second line
c. Ustekinumab in the first line, tofacitinib in the second line
d. Vedolizumab in the first line, tofacitinib in the second line
e. Vedolizumab in the first line, ustekinumab in the second line
f. Vedolizumab in the first line, anti-TNF-α in the second line
g. Anti-TNF-α in the first line, ustekinumab in the second line
h. Anti-TNF-α in the first line, vedolizumab in the second line
i. Anti-TNF-α in the first line, tofacitinib in the second line
j. Tofacitinib in the first line, ustekinumab in the second line
k. Tofacitinib in the first line, anti-TNF-α in the second line
l. Tofacitinib in the first line, vedolizumab in the second line

By the route of anti-TNF-α administration

a. Subcutaneous administration
b. Intravenous administration

Depending on surgical treatment within ≤ 2 years before biological therapy prescription:

a. Surgical patients
   - With post-operative anti-relapse biological therapy (CD)
   - Without post-operative anti-relapse biological therapy (CD)
b. Non-surgical patients

Depending on response to immunosuppressive therapy

a. Absence or loss of response

b. Maintenance of response

Depending on the age of onset:

a. < 18 years

b. 18–40 years

c. 41–60 years

d. 60 years

Depending on age at the time of inclusion in the study:

a. ≤ 60 years

b. 60 years

Depending on Body Mass Index

a. < 18.5 kg/m^2

b. 18.5–24.9 kg/m^2

c. 25–29.9 kg/m^2

d. 30–34.9 kg/m^2

e. 35–39.9 kg/m^2

f. ≥ 40 kg/m^2

8 STATISTICAL DATA PROCESSING

8.1 Statistical methods

8.1.1 General information

Statistical analysis will be conducted using the software package Microsoft R Open version 4.0.2 from Microsoft R Application Network (MRAN) (https://mran.microsoft.com). Exact version of the software will be determined at the time of first interim analysis and will remain unchanged throughout the study. Version control for the software and related R packages used for statistical data processing will be performed using the CRAN Time Machine from Microsoft (or the purpose of reproducibility, MRAN hosts daily snapshots of the CRAN R packages and R releases as far back as Sept. 17, 2014). Statistical analysis will take data type and scale for each parameter when describing and analyzing the data.

Quantitative data (both continuous and discrete, if applicable) will be presented using the following parameters:

- Number of non-missing observations (n);
- Arithmetic mean (M);
- Standard deviation (SD);
- 95% confidence interval for the mean (95% CI);
- Median (Me);
- 25th percentile;
- 75th percentile;
- Minimal value (min);
- Maximal value (max);

Qualitative data including binary and categorical variables will be presented as number of cases per category, frequency for the category (relative to the non-missing number of observations), as well as 95% exact binary confidence interval calculated using Clopper-Pearson method (binary data) or Goodman method (categorical data).

Time-to-event data will be presented as median, 25^{th} and 75^{th} percentiles as well as graphically as Kaplan-Meyer survival curves with log-log 95% confidence intervals.

No statistical tests are planned for the primary endpoint of this study as all outputs will be purely descriptive. However, 95% significance level will be applied for all confidence intervals calculated, and exploratory statistical analysis will be conducted to identify statistically significant associations between treatment patterns and outcomes.

Medical history, concomitant conditions and adverse events will be coded using the MedDRA dictionary. As version of MedDRA is updated every six months, the first interim analysis will be conducted using the most current MedDRA version, and all subsequent analyses, including the

final analysis, will be performed using the updated MedDRA versions and all previously analyzed data will be checked using MedDRA version comparison tool for the presence of changes from version to version and re-coded if applicable. The updated version of MedDRA used in the final analysis will be specified in the SAR. Both original and updated coding will be kept for tracking purposes.

Concomitant and prior medications will be coded with Anatomical Therapeutic Chemical Dictionary (ATC) current version.

Due to the descriptive nature of the study, all available data will be analyzed.

8.1.2 Assessment of primary endpoint

Treatment combinations will be described for UC and CD separately based on the following criteria:

1) Various types of biological and non-biological treatments including the following treatment combinations:
    a. Steroid[1] monotherapy (by class)
    b. Steroids (by class) + immunosuppressive therapy (by class) combinations
    c. Immunosuppressive monotherapy (by class)
    d. Immunosuppressive (by class) + 5-aminosalycilic acid derivatives (by class)
    e. 5-aminosalicylic acid derivatives monotherapy (by class)
    f. TNF-alpha inhibitor monotherapy (by trade name)
    g. TNF-alpha inhibitor therapy (by trade name) + steroids (by class)
    h. TNF-alpha inhibitor therapy (by trade name) + immunosuppressive therapy (by class)
    i. TNF-alpha inhibitor therapy (by trade name) + immunosuppressive therapy (by class) + steroids (by class)
    j. Vedolizumab monotherapy (by INN)
    k. Vedolizumab therapy (by INN) + immunosuppressive therapy (by class)
    l. Vedolizumab therapy (by INN) + steroids (by class)
    m. Vedolizumab therapy (by INN) + immunosuppressive therapy (by class)+ steroids (by class)
    n. Janus kinase (JAK) inhibitor monotherapy (by trade name)
    o. JAK inhibitor therapy (by trade name) + steroids (by class)
    p. JAK inhibitor therapy (by trade name) + immunosuppressive therapy (by class)
    q. JAK inhibitor therapy (by trade name) + immunosuppressive therapy (by class) + steroids (by class)

[1] Steroids will be standardized through the calculation of prednisolone equivalent dose to facilitate comparisons between the classes

Disclaimer: due to the observational nature of the study, it is impossible to predict the distribution of treatment patterns before the actual analysis is performed. The list above can be modified based on the actual study data by excluding of certain combinations (absent in the database or identified in less than 25 subjects) or by including the combinations that were not initially planned but were identified in the actual study database.

Treatment pattern will include unique combination of certain treatments or treatment combinations along with their change over time.

Each treatment combination will be analyzed using the following summary data:

- Average course duration;
- Average maximum dose for each component of the combination (across all courses);
- Average number of courses per patient;
- Total duration of use of each combination / course for the total duration of observation retro- and prospective);
- Distribution of each pattern by subgroups: age, gender, region, duration of the disease, disease activity (according to Visit 1 Mayo / Harvey-Bradshaw indices).

8.1.3 Assessment of secondary and exploratory endpoints

Each original treatment combination (defined as the treatment combination that was used by the patient at the very start of retrospective observation period, i.e. first recorded treatment combination in the study) will be tabulated by the below listed parameters using the generic table format below (see example tables: Table 10, Table 11, Table 12 and Table 6):

- Demographic data;
- Disease activity at Visits 1, 2 ,3 (Mayo, Harvey-Bradshaw indices);
- Disease status assessed by investigator at Visits 1, 2, 3;
- Frequency (percentage) of clinical, endoscopic and histologic remission at Visits 1, 2, 3 and retrospective period of observation;
- Extent of lesion at Visits 1, 2, 3;
- Systemic (extraintestinal) manifestations at Visits 1, 2, 3;
- Total number, duration and severity of disease exacerbations by Visit 1, 2 and 3;
- Total number, type and duration of disease complications by Visit 1, 2 and 3;
- Laboratory and instrumental assessments at Visits 1, 2, 3;
- Percentage of patient with surgical treatment by Visits 1, 2, 3 grouped by:
    - Indication;
    - Surgery type;
    - Presence of complications.
- Number of surgeries by Visits 1, 2, 3;

- Percentage of patients with at least on episode of failure or biological or/and non-biological therapy (e.g., dose escalation of biologics, switching to another therapy, IBD-related surgery, medication augmentation) by Visits 1, 2 and 3;
- Separately for patients who achieved / not achieved T2T treatment goals (based on the clinical assessment of IBD) by Visits 1, 2 and 3:
    - Presence of therapeutic de-escalation;
    - Presence of therapeutic escalation;
    - Continuation of therapy without any changes.
- Healthcare resources utilization:
    - Hospitalizations due to complications;
    - IBD-related surgeries;
    - Percentage of patients that used healthcare resources;
- Only for biological therapy - percentage (by Visits 1, 2, 3) of patients with:
    - Positive test results for TB before the start of biological therapy;
    - Active TB before the start of biological therapy;
- Percentage of patients by Visits 1, 2, 3 with:
    - Reactivation of TB;
    - New occurrence of TB.

The same information will be provided for the treatment pattern (if the corresponding treatment pattern will be large enough to make statistical inferences).

As treatment pattern change over time, patterns will be assessed for certain time points and the change of patterns will be tracked throughout the study (see also example Table 8):

- Retrospective treatment pattern (change assessment for every 6 months of the 2-year treatment interval);
- Treatment pattern between the date of enrollment and 6 months;
- Treatment pattern between 6 and 12 months.

Accordingly, for each above-mentioned period, each pattern will be assessed for the history of changes (see example Table):

- Presence of dose modifications;
- Presence of discontinuations / treatment changes;
- Presence of flares (during the course of treatment);
- Add-on therapy.

In order to track the history of transition of subject "states" (i.e. treatment using the certain pattern from the list above), in addition to the descriptive 6-monthly data, transition state (Sankey) diagrams will be built (see Figure 2 for mock example) to visualize the subject journey across patterns as well as trends of pattern change over time.

Treat-to-target (T2T) success will be assessed (in this SAP) using EDC data, based on the definition of failure to meet T2T goals *(lack of clinical and endoscopic remission based on investigator's feedback and objective methods of evaluation)*. Overall T2T success or failure will be analyzed separately from this SAP using Investigator Survey data.

T2T treatment factors will be assessed by Visits 1, 2 and 3 and will be grouped by:

- Clinician-related factors:
  - Frequency and methods of assessment of UC/CD disease activity;
- Patient-related factors:
  - Demographic data;
  - Time frame between the date of first symptom(s) and the date of IBD diagnosis;
  - Smoking status;
- Disease-related factors:
  - Age of disease onset;
  - Location of disease;
  - Clinical course;
  - Disease severity;
  - Presence of intestinal and systemic (extraintestinal) manifestations;
  - Presence of complications;
  - Surgical treatment.

8.1.4 Data tabulation principles

All data will be presented descriptively for each defined treatment pattern and can be further divided into subgroups depending on the presence of certain factors of interest in data (see section 7.4).

All summary tables will be structured with a column for each pattern in the defined order and will be annotated with the total population size relevant to that pattern, including any missing observations relevant for the particular table.

8.1.5 Safety data analysis

Collection of safety data starts with the signing of ICF for this study, so, there will be no safety data available for the retrospective part of the study.

Safety data will be presented for the population of all patients enrolled as well as for each defined treatment combination (or pattern, if applicable) separately. Data will be presented as total counts as well as distribution by SOC at Visits 1, 2 and 3:

- Overall frequency of all AEs;
- Frequency of all AEs that led to treatment discontinuation / treatment change regardless of their relation to a particular medication;
- Frequency of SAEs;
- Frequency of all SAEs that led to treatment discontinuation / treatment change regardless of their relation to a particular medication;
- Frequency of ADRs;
- Frequency of SADRs;
- Frequency of pregnancy cases.

Additionally, all AEs/SAEs and ADRs/SADRs will be tabulated according to their relation to a particular medication (see example Table 17), separate tables will be generated for each medication being a monotherapy and in treatment combination.

8.1.6 Listing generation principles

All data will be listed, sorted by site and patient, and when appropriate by visit number within patient. As described in ICH E3 guidelines, each listing will include patient's demographics (age and gender) for ease of reading and interpretation. Listings can be saved in Excel sheets.

8.2 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-bio logical 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 and that 40-50% of the patients on biological therapy will have at least one episode of treatment failure during 12 months, enrolment of 3000 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 (±4.7% 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.

Table 2. Sample size and corresponding precision of estimate

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 biological therapy**	
			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.*

8.3 Applicable significance level

Analysis will be performed in a descriptive manner, so, there will be no applicable statistical tests. However, 95% confidence intervals will be calculated for means and proportions, so, 95% significance level will be applied that corresponds to 5% alpha (type I) error.

As there are no statistical tests applied to any of the tabulated data, there will be no multiplicity (multiple comparison) corrections applied to the significance level.

8.4 Handling of missing or incorrect data

Assigned data manager and statistician will continuously identify missing, questionable or non-interpretable data in the study database, and queries will be generated to study sites to address this.

All missing, questionable or non-interpretable data that were not clarified through query generation process will be treated as missing and not included in the final statistical database for interim and final analyses. Listing of such data will be provided as an attachment to the statistical analysis report, if applicable.

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

8.5 Procedures for reporting of any deviations from the initial statistical analysis plan

Any decision to change statistical analysis plan that will contradict the protocol, should be approved by study Sponsor. Final study report should contain all changes made compared to the original statistical analysis plan with the appropriate justification of such changes.

8.6 Analysis populations (data sets)

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 summarized after data base cleaning and lock.

All planned analyses (including descriptive analyses and study listings) will be performed for Full Analysis Set (FAS) of data.

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

- **All Patients Enrolled population (equal to FAS):** All patients who signed informed consent to enter the study.

Subjects that were enrolled with the violation of inclusion and subsequently withdrawn from the study (upon recognition of such violation) will be excluded from FAS and analyzed separately for baseline characteristics only (the decision whether to analyze such patients in the interim analysis will be defined by the number of such patients – summary data will be presented if this subgroup is >10 observations).

- **Safety population:** Patients who have taken at least one dose of any IBD medicine after enrolling in the study (Baseline visit).

Due to observational nature of the study, and possible presence of missing data for analysis, it is possible to exclude several patients or the entire study center at the analysis stage.

8.7 Interim analysis

Two interim analyses are planned – in 2019 and 2020 – with corresponding interim data locks for the completed cases:

- 2019: about 700 completed cases for retrospective data analysis
- 2020[2]: 3000 completed cases for retrospective and partial prospective data (up to 6 months)

[2] According to the current version of the protocol, the set of collected data has been reduced to 2000 cases. Therefore, the second analysis (second look) of data was not performed in 2020.

All cases will be included into interim analysis with the prerequisite of complete data cleaning, i.e., corresponding eCRF forms are complete, free of any pending queries and signed by the corresponding investigator.

Retrospective data analysis (2019): will include the following endpoints (all endpoints will be assessed retrospectively for the period of 2 years of retrospective data collection):

1) Treatment patterns associated with prior biologic agents use or non- biological therapy according to the algorithm provided in the section 8.1.2);
2) Demographic data, medical history, treatment history, concurrent diseases, concomitant medications by treatment group/pattern;
3) Demographic data for FAS;
4) Family history of IBD, smoking habits, medical history comorbidities for FAS;
5) Disease characteristics: age of disease onset, location of disease, clinical course, disease severity, intestinal and systemic (extraintestinal) manifestations, complications in history for FAS;
6) Frequency and methods of assessment of UC/CD disease activity;
7) Assessment of healthcare resource utilization;
8) TB incidence and prevalence in IBD patients by treatment pattern;
9) TB medication's use in IBD patients by treatment pattern;
10) Compliance between the assessment of IBD status by investigator and objective methods of assessment (Mayo index, Harvey-Bradshaw index, instrumental assessments).

No safety analysis will be performed for the retrospective data analysis as there will be no safety data in the retrospective part of the study.

Retrospective and partial prospective data analysis (2020): will include the following endpoints (main endpoints will be assessed retrospectively for the period of 2 years of retrospective data collection and for the 6 months of the prospective data collection; safety endpoints will be assessed for prospective part of the study only):

1) Treatment patterns associated with prior biologic agents use or non-biological therapy according to the algorithm provided in the section 8.1.2);
2) Demographic data, medical history, treatment history, concurrent diseases, concomitant medications by treatment group/pattern;
3) Frequencies and time to achieve remissions and exacerbations by treatment group/pattern;
4) Frequency and methods of assessment of UC/CD disease activity;
5) Assessment of healthcare resource utilization;

6) Probable causes preventing achieving T2T targets during routine care;
7) The extent to which proposed Treat to Target goals are achieved by treatment group/pattern;
8) TB incidence and prevalence in IBD patients by treatment pattern;
9) TB medication's use in IBD patients by treatment pattern;
10) Adverse drug reactions (ADRs) on IBD treatments;
11) Adverse events on Entivyo® (vedolizimab) treatment;
12) Serious adverse events on IBD treatments (including Entivyo® (vedolizumab) treatment).

As there are no statistical hypotheses tested, there will be no alpha spending function correction applied to the interim analysis.

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