Clinical Study Protocol

EU PAS Number: EUPAS34232

Title: Association Between Disease Activity and QoL, Fatigue, Mood and Sleep Disorders in Patients with Moderate to Severe Ulcerative Colitis or Crohn's Disease Treated with Vedolizumab - A Prospective, Observational Study Based on Patient Reported Outcomes

Study Number: Vedolizumab-5060

Document Version and Date: 2.0 (09 February 2022)

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

Non-Interventional Study Protocol

Title: Association between disease activity and QoL, fatigue, mood and sleep disorders in patientswith moderate to severe Ulcerative Colitis or Crohn's Disease treated with vedolizumab - a prospective, observational study based on patient reported outcomes.

Short title: KUJAWIAK study

Study ID: Vedolizumab-5060

Protocol version: 2.0

Sponsor: Takeda Pharma Sp. z o.o.
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Study phase: Medical Affairs, Post-Approval Company Sponsored (Observational)

Date of version 2.0 **of protocol:** 09 Feb 2022

1 Administrative information

1.1 Contacts

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

Study Lead	[redacted] Takeda Polska sp. z o.o. Warszawa Ul Prosta 68 Tel: [redacted]
Responsible Medical contact (carries overall responsibility for the conduct of the study)	[redacted] Takeda Polska sp. z o.o. Warszawa ul. Prosta 68 Tel: [redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

Takeda Pharma sp z o.o. Date

Takeda Pharma sp. z o.o. Date

INVESTIGATOR SIGNATURE PAGE

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

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

Signature of Investigator Date

<Investigator Name (print or type)>

<Investigator's Title>

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

<Location of Facility (Country)>

STUDY SUMMARY

<table>
<tr><td>Name of Sponsor(s):
Takeda Pharma sp z o.o.</td><td>Compound/Product:
Vedolizumab/Entyvio</td></tr>
<tr><td colspan="2">Title of Protocol: Association between disease activity and QoL, fatigue, mood and sleep disorders in patients with Ulcerative Colitis or Crohn’s Disease treated with vedolizumab - a prospective, observational, multicenter study.</td></tr>
<tr><td>Study Number: Vedolizumab-5060</td><td>Phase: IV</td></tr>
<tr><td colspan="2">Study Design:
KUJAWIAK is a prospective, multicenter, observational, open-label study designed to document the management and clinical outcome of patients with Ulcerative Colitis or Crohn’s Disease based on real-world data. There is no predefined sample size.</td></tr>
<tr><td colspan="2">Primary Objectives:
1. To determine effect of vedolizumab on QoL measured at week 14 (end of induction therapy in the Drug Program).</td></tr>
<tr><td colspan="2">Secondary Objectives:
1. To determine the short-term effectiveness of vedolizumab in induction measured at week 14.
2. To determine the effect of vedolizumab on fatigue measured at week 14.
3. To determine the effect of vedolizumab on mood and sleep disorders at week 14.
4. To determine real-world safety of vedolizumab.</td></tr>
<tr><td colspan="2">Exploratory Objectives:
[redacted]
3. To describe UC/CD patients’ demographic and clinical characteristics.</td></tr>
<tr><td colspan="2">Subject Population: Consecutive IBD (UC or CD) adult (aged ≥18) outpatients attending the gastroenterology clinics in Poland scheduled for vedolizumab infusion in the scope of Drug Program between Sep 2020 – Mar 2022 for UC patients and between Sep 2020 and Jul 2022 for CD patients.</td></tr>
<tr><td>Number of Subjects:
All adult patients qualified to CD or UC Drug Program between Sep 2020 and Mar 2022 for UC patients and between Sep2020 and Jul 2022 for CD patients.</td><td>Study Sites:
Approximately 15 Gastroenterology Clinics in Poland to be enrolled in the KUJAWIAK study</td></tr>
<tr><td>Dose Level(s):
Vedolizumab to be administrated in accordance to SmPC and Drug Program.</td><td>Route of Administration:
Vedolizumab to be administrated intravenous in accordance to SmPC.</td></tr>
<tr><td colspan="2">Duration of Study:
Overall Study Duration: 29 months
Enrolment period: 19 months for UC patients, 23 months for CD patients
Treatment/Follow-up: 3.5 months (14 weeks)</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:</td></tr>
</table>

1. Adult (aged ≥18) UC or CD patients qualified to be treated with vedolizumab in the scope of Drug Program. 2. Patients willing to participate in the study and signed ICF.
Main Criteria for Exclusion: 1. Patients currently participates or plans to participate in any interventional clinical trial. 2. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.
Statistical Considerations: Data will be summarized using standard descriptive statistics. For primary and secondary endpoints appropriate statistical tests will be applied (paired Student t-test or Wilcoxon signed-rank test), while percentages will be presented with 95% confidence intervals. Moreover, for exploratory objectives linear mixed effect models and logistic regression models will be used.
Sample Size Justification: There is no predefined sample size, and all data collected during KUJAWIAK study will be considered for analytical purposes. Alternative analyses may employ sample sizes based upon sub-populations.

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Appendix 1 Data collection overview

Appendix 2 Drug Program UC and CD

Appendix 3 Summary of changes

List of Abbreviations and Definition of Terms

Abbreviation or special term	Explanation
6-MP	6-mercaptopurine
AE	adverse event
AESI	adverse event(s) of special interest
CD	Crohn's disease
CRP	C Reactive Protein
DP	Drug Program
eCRF	electronic case report form
GCP	Good Clinical Practices
GEP	Good Epidemiology Practices
GI	gastrointestinal
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
hsCRP	high sensitivity C Reactive Protein
IBD-Q	inflammatory bowel disease questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
NLVSS	Number of Liquid or Very Soft Stools
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SmPC	Summary of Product Characteristics
UC	ulcerative colitis
VDZ	vedolizumab

2 Introduction

IBD often adversely affects QoL. Chronic nature of disease, frequent recurrence of symptoms, extraintestinal manifestations, the effect of medical and surgical treatments, stress of developing cancer may have strong impacts on patients life and cause reduction in quality of life. There are premises that inflammatory activity can be important factor which affects QoL in IBD patients (Kim WH, 1999; Zahn A, 2006) .

One of the most challenging symptoms with high prevalence that can impact HRQOL in IBD patients is fatigue. Fatigue can be as problematic as diarrhea and abdominal pain because it may be severe, and not necessarily correlated with disease activity. IBD-related fatigue can also be frequently observed in patients in disease remission (Drossman DA, 1989). The reported prevalence of fatigue in IBD ranges from 29% to 41% during clinical remission and from 57% to 72% during active disease (Villoria A, 2017).

Poor sleep quality is common in patients with active and inactive IBD. It was observed that poor sleep quality and disease activity are correlated. Patients in clinical remission with abnormal sleep have a high likelihood of having histologically active disease (subclinical disease activity). Moreover, sleep disturbance has relations with fatigue during day, mood, depression, and more physical symptoms. In the general population, persistent insomnia has been associated with higher risk of developing clinical anxiety or depression (Ali T, 2014; Habib F, 2017).

This is non-interventional study aiming to assess whether vedolizumab treatment can promptly (14 weeks of induction) impacts QoL, fatigue and mood and sleep in Polish adult patients with ulcerative colitis or Crohn’s disease.

Having in regards that recruitment period in KUJAWIAK study is 19 months for UC patients and 23 months for CD patients it is expected that total study population will be approximately 300 patients, including UC and CD patients. Data collected from such a high number of patients can be truly valuable not only with regards to short-term effectiveness and safety in real-world setting, but also in regard to early appearing signs of response measured by PROs.

3 Study Objective(s)

3.1 Objective(s)

3.1.1 Primary Objective

1. To determine effect of vedolizumab on QoL measured at week 14 (end of induction therapy in the Drug Program).

3.1.2 Secondary Objective(s)

1. To determine the short-term effectiveness of vedolizumab in induction measured at week 14
2. To determine the effect of vedolizumab on fatigue measured at week 14.
3. To determine the effect of vedolizumab on mood and sleep disorders at week 14.
4. To determine real-world safety of vedolizumab.

3.1.3 Exploratory Objective(s)

[redacted]

3. To describe UC/CD patients' demographic and clinical characteristics

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in approx. 15 sites in Poland. The sites in KUJAWIAK study will be hospitals and clinics administarting vedolizumab in the frames of Drug Program.

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

4.2 Sponsor Personnel

Sponsor will keep a record of all relevant Sponsor personnel that will be responsible for study oversight.

4.3 Contract Research Organisation (CRO)

The CRO, Biostat Sp. z o.o., ul. Kowalczyka 17, 44-206 Rybnik, Poland will be in charge of data management, Statistical Analysis Plan, analysis and generation of a study report. Data management tasks will be conducted according to the CRO's SOPs. Sponsor or CRO will also be in charge of relevant document submission to Independent Ethics Committee (IEC). Details of the tasks and responsibilities are regulated in the contract between the Sponsor and the CRO. The CRO will keep a record of all involved CRO personnel.

5 Ethics

This study is an observational study where the existence of the study has no impact on the subject except for collection of informed consent to use of the subject's data and to collect data from patients' questionnaires.

5.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Special attention will be paid to data protection. Special attention will be paid to data protection as described in Directive 95/46/EC.

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

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

5.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/ IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Subject Information Sheet / Informed Consent Form, patients questionnairies, eCRF printout.

The appointed CRO or the Site Study Responsible will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study (if appicable)
- notification of the end-of-study
- a summary of the study results

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

5.3 Subject Information and Written Informed Consent

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

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

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.
The subject and parent or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.

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

6 Study Design and Plan

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

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.
- Vedolizumab is prescribed in accordance with the terms of the marketing authorisation(s)
- The prescription of vedolizumab is clearly separated from the decision to include the subject in the study

Prospective, observational (non-interventional), multicentre study with consecutive patients aged ≥ 18 enrolled between Sep 2020 and Mar 2022 with ulcerative colitis or between Sep 2020 and Jul 2022 with Crohn's disease fulfilling inclusion criteria to Drug Program. To avoid overlap with recruitment of Crohn's disease patients into another Takeda sponsored observational study POLONEZ II (Vedolizumab 5056), particularly in sites engaged in both

projects, patients for KUJAWIAK study will be recruited in two waves. Enrolment of ulcerative colitis patients will commence in Sep 2020 as a first wave and patients with Crohn's Disease may begin just after last patient is recruited into POLONEZ II study.

Data collection is scheduled in line with Drug Program visits and will not cause any further obligations for the patients except of signing ICF and filling patients' questionnaires.

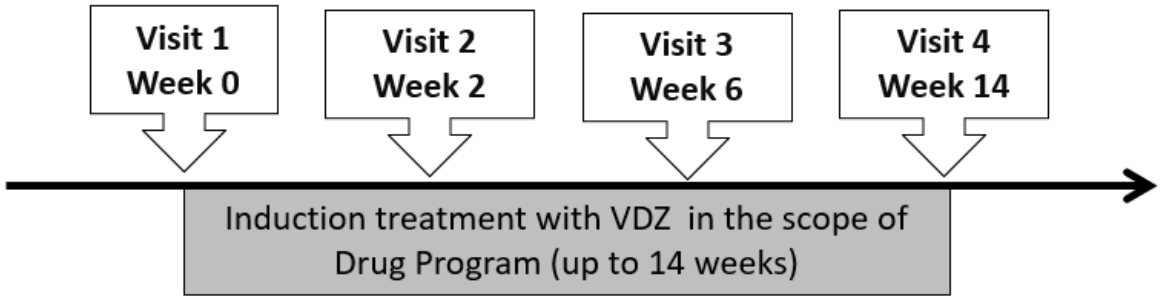

Fig.1 Study design

There are 4 visits scheduled in the study framework (week 0, week 2, week 6 and week 14) (Fig. 1).

Disease activity and response to the treatment with vedolizumab will be assessed with standard measure such as Mayo Score or CDAI in UC and CD patients respectively, what is in line with DP requirements.

Additionally, each patient will be asked to fill a following questionnaires:

1. FACIT-Fatigue
2. Inflammatory Bowel Disease Questionnaire (IBDQ)
3. PROMIS Depression
4. PROMIS Sleep Disturbance

Questionnaires to be filled before VDZ dose administration at V1, V2, V3 and V4.

6.1 Study Schedule

Planned Start of Study:	Sep 2020
Planned collection of first data point:	Sep 2020
Planned End of Study:	Jan 2023
Planned collection of the last data point:	Jan 2023
Planned completion of the Study Report:	Apr 2023

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

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

6.2 Discussion of Study Design

KUJAWIAK is a non-interventional study (NIS), designed to generate real-world evidence (RWE), complement and provide additional insight to the data produced through clinical trials. NIS are critical for assessing utilization, treatment patterns, comparative effectiveness and safety, and providing overall value demonstration, as well as informing on important therapeutic findings to help guide treatment decisions and real-world use. Having in regards that in KUJAWIAK study, patient's data are gathered and collected during routine clinical care, there will be single arm only with no control (no randomization). Potential source of bias in non-interventional studies is well-known and it is equal to KUJAWIAK study, however prospective nature of the study, multi-centres involved and expected high number of enrolled patients must be highlighted as factors distinguishing KUJAWIAK study.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.

2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. Patients qualified to vedolizumab treatment in the scope of Drug Program between Jun 2020 and December 2021 and receive treatment according to the Summary of Product Characteristics for Entyvio.
4. Male or female subjects, aged ≥ 18 years.

6.3.2 Exclusion Criteria

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

1. Currently participates or plans to participate in any interventional clinical trial.
2. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

Subjects should be included in the study only once.
Data erroneously collected from subjects for which written consent is not available, will not be included in or will be deleted from the database.

6.4 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol.

6.5 Premature Termination or Suspension of Study or Investigational Site

6.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the vedolizumab and may have serious impact on treatment effectiveness or patients safety.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

6.6 Study Plan

Data collection overview:

	Visit1 (Week 0)	Visit 2 (Week 2)	Visit 3 (Week 6)	Visit 4 (Week 14)	Early Termination visit
Informed consent	X				
Data collection (for details see section 8.4.1)	X			X	X
IBDQ	X	X	X	X	
FACIT-Fatigue	X	X	X	X	
PROMIS Depression questionnaire	X	X	X	X	
PROMIS Sleep disturbance questionnaire	X	X	X	X	
Safety reporting	X	X	X	X	X

7 Safety Reporting

7.1 Definitions

Adverse Event

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

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

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

Serious Adverse Events

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

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

of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Drug Reactions

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

Product Quality Issues

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

Special Situation Reports

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

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

A SSR should be reported even if there is no associated AE.

Relationship of an AE to studied drug(s)

- **Related (Yes):** An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), or for which a casual relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- **Not related (No):** An AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments. The investigator must make an assessment of causality using the above definition. Causality cannot be assumed in the absence of the investigator's assessment.:

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

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be notified to the local Takeda Pharmacovigilance department within 1 working day for SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

8 Data Quality Control and Assurance

8.1 Quality Control

A web-based application (eCRF) will be used for entering data into the Kujawiak database, allowing for remote data entry at hospital/investigator centers. The users will access the Kujawiak database via a web browser. A dedicated database server stores all the information collected from the clinics participating in Kujawiak study. The database server is managed by an independent external service provider to ensure that the data are kept secure and confidential during data collection, transfer and storage.

The Kujawiak eCRF is described in the eCRF manual, which will be provided to each participating center and can be accessed within the database. Immediate questions or problems with the data entry that are not addressed in the eCRF manual may be directed to representatives of Takeda/Biostat (CRO).Note that this study has core variables that must be completed in the registry in order for a specific visit data entry to be considered "complete." Please see Appendix 3 for the list of core variables.

In order to ensure good quality, patient source data should be available by direct access, at individual centers, for the routine monitoring visits done by Takeda designated contract research organization. It is important that the responsible Kujawiak investigator and other relevant personnel are available during these monitoring visits, and that sufficient time is allocated. Kujawiak study will also be monitored remotely by designated CRO. The nature and frequency of the monitoring will be dependent on the number of patients enrolled at each individual center and will be presented in dedicated Monitoring Plan.

8.2 Audit from Quality Assurance Unit

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

8.3 Inspection by IRB/IEC

Representatives from IRB/IEC may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately

contact Global Research and must make the records available as requested. The Inspector must be reminded up front that consent to access to personal data has not been obtained from the participants in this study.

8.4 Data Management

Biostat (CRO) is responsible for Data Management. Data Management will be carried out according to a Data Management Plan, which must be written and approved before the design of the study database is finalised. The data management provider should approve all data formats before the data collection tools are made available to the sites.
If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

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

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

The subjects will be identified in the database only by Study ID, Site ID, subject number, date of birth, gender.

8.4.1 Data Collection Tools and Flow

The Study Sites will receive access to Electronic Data Collection System (EDC) allowing for collection of eCRF from Takeda/Biostat. Sites will receive training and have access to a manual for appropriate CRF completion. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should follow the requested language standard.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 7 and data on serious AE/ADR reactions collected according to section 6 should be signed off separately by a physician who may or may not be involved in the study. The eCRFs will be submitted electronically to Biostat and will be handled in accordance with study Data Management Plan. Data will be periodically transferred electronically from the Biostat to Takeda, and the Biostat's standard procedures will be used to handle and process the electronic transfer of these data. At the end of the study, participating investigators will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

The eCRFs and correction documentation will be maintained in the EDC system audit trail.

System backups for data stored by Biostat and records retention for the study data will be consistent with the Takeda and CRO standard procedures. Biostat will comply with the Takeda's procedures regarding archiving and record management.

9 Statistical Methods and Determination of Sample Size

Statistical analysis will be performed by Biostat Sp. z o. o. . follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9 as well as Biostat's SOPs.

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 will be described in a revised Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the Clinical Study Report.

All data collected will be analyzed descriptively. Standard descriptive statistic methods will be applied including number of patients, arithmetic mean, standard deviation, upper and lower quartiles, minimum, median and maximum. For categorical variables frequencies and percentages (absolute and relative frequencies) will be presented.

Selected endpoints pertaining to secondary and exploratory objectives will be tested. Due to interim analysis O'Brien-Fleming approach will be used for controlling the type I error – significance level will be equal to 0.0054 for the interim analysis and 0.0492 for the final analysis.

Scope and methodology of statistical tests will be described in the statistical analysis plan (SAP), a separate document provided by the CRO.

The safety endpoints will be presented as incidence rate calculated using person-time analyses. The safety analysis set will include all subjects treated with vedolizumab. Reported adverse events will be coded using MedDRA dictionary (version current at the time of study initiation) and all adverse event summaries will present preferred terms and System Organ Class. Where appropriate 95% confidence intervals will be provided.

9.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data (listed in 6.6 and Appendix 1 Data collection overview), except variables collected only for the purpose of data cleaning. All analyses will be performed separately for UC and CD patients.

The main outcomes of the study are:

- Change from baseline to end of induction therapy in the Drug Program (week 14) in IBDQ total score; change from baseline to end of induction therapy in the Drug Program (week 14) in IBDQ domain scores (for bowel symptoms, systemic symptoms, emotional function and social function).
- Proportion of patients experiencing response (defined as an increase in the IBDQ total score of ≥ 16 points at the end of induction therapy) in the Drug Program (week 14).

Secondary outcomes of the study are:

- Proportion of patients experiencing clinical response (defined as a reduction in CDAI score of at least 70 points and at least 25% from baseline for CD patients and reduction in disease activity by at least 3 points on the Mayo sore for UC patients) to vedolizumab treatment at the end of induction therapy in the Drug Program (week 14).
- Change from baseline to end of induction therapy in the Drug Program (week 14) in frequency and severity of fatigue (measured using FACIT-F Section 1 total score).
- Change from baseline to end of induction therapy in the Drug Program (week 14) in impact of fatigue on individuals' lives (measured using FACIT-F Section 2 total score).
- Change from baseline to end of induction therapy in the Drug Program (week 14) in depression expressed as value of T-score calculated from PROMIS Depression questionnaire.
- Change from baseline to end of induction therapy in the Drug Program (week 14) in sleep disturbance as value of T-score calculated from PROMIS Sleep disturbance questionnaire.

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

Primary analysis:

- Change from baseline to end of induction therapy in the Drug Program (week 14) in IBDQ total score as well as domain scores will be tested using either a paired Student t-test or Wilcoxon signed-rank test[1] and presented with appropriate descriptive statistics and 95% CI.
- Proportion of patients experiencing response (defined as an increase in the IBDQ total score of ≥ 16 points at the end of induction therapy in the Drug Program (week 14) will be presented with 95% CI.

Secondary analyses:

- Remission rates at the end of 14-week induction period will be presented as proportion with 95% Confidence Interval
- Change from baseline to end of induction therapy in the Drug Program (week 14) in frequency and severity of fatigue (measured using FACIT-F Section 1 total score) will be tested using either a paired Student t-test or Wilcoxon signed-rank test and presented with appropriate descriptive statistics and 95% CI
- Change from baseline to end of induction therapy in the Drug Program (week 14) in impact of fatigue on individuals' lives (measured using FACIT F Section 2 total score) will be tested using either a paired Student t-test or Wilcoxon signed-rank test and presented with appropriate descriptive statistics and 95% CI
- Change from baseline to end of induction therapy in the Drug Program (week 14) in depression expressed as value of T-score calculated from PROMIS Depression

[1] In all situations choice between Student t-test or Wilcoxon signed-rank test will depend on result of normality verification.

questionnaire) will be tested using either a paired Student t-test or Wilcoxon signed-rank test and presented with appropriate descriptive statistics and 95% CI

- Change from baseline to end of induction therapy in the Drug Program (week 14) in sleep disturbance as value of T-score calculated from PROMIS Sleep disturbance questionnaire) will be tested using either a paired Student t-test or Wilcoxon signed-rank test and presented with appropriate descriptive statistics and 95% CI
- Safety evaluation will be performed on AEs, SAEs and pregnancy outcomes collected in adverse event form. Reported adverse events will be coded using MedDRA dictionary (version current at the time of study initiation) and all adverse event summaries will present preferred terms and System Organ Class. The safety endpoints will be presented as incidence rate calculated using person-time analyses. The safety analysis set will include all subjects treated with vedolizumab (SAF population). Where appropriate 95% Poisson confidence intervals will be provided.

Exploratory analyses:

- Primary and secondary analyses will be performed taking into account patients' disease (UC or CD). Briefly, a difference between baseline and week 14 in questionnaire scores will be compared between patients with UC and CD.

[redacted]

For details of the statistical analyses please refer to the Statistical Analysis Plan.

9.2 Interim Analyses

Interim analysis to be performed in the middle of recruitment period (8-9 months after start of data collection). The results from Interim Analysis will be published in a medical journal. All

primary, secondary and exploratory analyses will be performed. As mentioned, O'Brien-Fleming approach will be used, and significance level will be set to 0.0054.

9.3 Determination of Sample Size

No predefined sample size has been assumed for this study, and all data collected during KUJAWIAK study will be considered for analytical purposes. Nevertheless, a potential for enrolment during recruitment period indicates that approximately 300 consecutive patients, including both UC and CD, fulfilling inclusion criteria and not meeting exclusion criteria will be recruited and observed.

10 Reports

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

11 Publication, Disclosure, and Clinical Trial Registration Policy

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

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

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

12 Archiving of Study Documentation

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

- Written agreement between the Sponsor representative – CRO, Study Site and Investigator.
- The study protocol and any amendments

- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible
- Subject Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required), including the original signed Forms
- The list of participating subjects
- Written IEC / IRB approval
- The completed CRFs
- The progress reports

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

13 References

1. World Medical Association Declaration of Helsinki. Ethical principles for Medical Research Involving Human Subjects, Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000, and Seoul 2008.
2. Epstein, M on behalf of ISPE. Guidelines for Good Pharmacoepidemiology Practices (GPP). Pharmacoepidemiology and Drug Safety 2005;14:589-95.
3. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data. Official Journal of the European Communities L281/31 23.11.1995.
4. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official JournaFl of the European Communities L/21/34 1.5.2001.
5. Ali T, O. W., 2014. Sleep disturbances and inflammatory bowel disease.. *Inflamm Bowel Dis.*, pp. 1986-1995.
6. Drossman DA, P. D. M. C. Z. E. A. M., 1989. Health-related quality of life in inflammatory bowel disease. Functional status and patient worries and concerns.. *Dig Dis Sci.*, pp. 1379-1386.
7. Habib F, H. M. G. A. e. a., 2017. Quality of life in inflammatory bowel disease patients: A cross-sectional study. *J Res Med Sci.*, pp. 1-7.
8. Kim WH, C. Y. Y. H. e. a., 1999. Quality of life in korean patients with inflammatory bowel diseases: Ulcerative colitis, crohn's disease and intestinal behçet's disease.. *Gastroenterol Res Pract*, pp. 52-57.
9. Villoria A, G. V. D. A. e. a., 2017. Fatigue in out-patients with inflammatory bowel disease: Prevalence and predictive factors. *Plos One*, pp. 1-12.
10. Zahn A, H. U. K. M. E. R. S. W., 2006. Health-related quality of life correlates with clinical and endoscopic activity indexes but not with demographic features in patients with ulcerative colitis. *Inflamm Bowel Dis*, pp. 1058-1067.

14 Appendices

Appendix 1 Data collection overview

1. Subject demographics
    a. gender
    b. age
    c. height, body weight, BMI
    d. smoking status current and passed,
    e. voivodship (area) of residence

2. Clinical characteristics of UC or CD
    a. Time of diagnosis/disease duration,
    b. Disease extent according to Montreal Classification
    c. Presence of EIMs such as:
        i. arthritis,
        ii. arthralgia,
        iii. ankylosing spondylitis,
        iv. erythema nodosum,
        v. pyoderma,
        vi. ocular symptoms (uveitis, scleritis),
        vii. PSC,
        viii. aphthous stomatitis.

    d. Hospitalizations in last 12 months due to UC/CD and cumulative number of days spent in hospital
    e. Course of disease treatment (steroid resistant, steroid dependent, steroid intolerance)
    f. Current treatment with steroids and immunomodulators (substance and daily dose)

3. Comorbidities, if present
    a. Autoimmune such as: RA, psoriasis, PSA, LE, autoimmune hepatitis, G-B disease, Hashimoto thyroiditis, multiple sclerosis, if any other - may be specified;
    b. Metabolic such as diabetes, if any other – may be specified,
    c. Any other comorbidity - may be specified

4. History of biologic treatment due to UC/CD with infliximab or its similars and its outcomes -
    a. specific drug used,
    b. dose received,
    c. effectiveness,
    d. dose escalation if occurred
    e. reason for discontinuation if occurred

5. Current treatment with vedolizumab in DP - overview
    a. Number of doses received so far,
    b. Reason for dose delay if occurred
    c. Infusion reaction if occurred
    d. AE/SAE if occurred

6. Assessment of vedolizumab effectiveness in MS or CDAI

7. Current non-biologic treatment includes following categories of drugs, including specific drug used, dose received:
    a. Immunomodulators: azathioprine or 6-mercaptopurine (6-MP)
    b. Corticosteroids (Prednizon or Metylprednizolon or Budesonid)
    c. Any iron supplementation
    d. Folic acid supplementation

8. Biomarkers:
    a. CRP/hsCRP)
    b. Hb
    c. RBC
    d. MCV
    e. MCH
    f. PLTs

Appendix 2 Drug Programs

TREATMENT OF PATIENTS WITH ULCERATIVE COLITIS (UC) (ICD-10 K51)

SCOPE OF GUARANTEED MEDICAL SERVICE		
MEDICAL SERVICE RECIPIENTS	**DOSING REGIMEN AS PART OF THE THERAPEUTIC PROGRAMME**	**DIAGNOSTIC TESTS PERFORMED AS PART OF THE PROGRAMME**
1. Inclusion criteria The following medical service recipients are eligible for infliximab treatment: aged 6 years and above, with diagnosed severe ulcerative colitis, in whom treatment with ciclosporin is not indicated or contraindicated, and: 1) with inadequate response to the standard treatment, including treatment with corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), (Mayo score > 6 in persons aged ≥ 18 years or PUCAI ≥65 in persons aged < 18 years), or 2) intolerant to treatment with corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or 3) having contraindications to treatment with corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA). The following medical service recipients are eligible for vedolizumab treatment: aged 18 years and above, with diagnosed severe ulcerative colitis, in whom treatment with ciclosporin is not indicated or contraindicated, and: 1) with inadequate response to the standard treatment, including treatment with corticosteroids and 6-mercaptopurine (6-MP) or	Dosage of infliximab/vedolizumab in ulcerative colitis treatment – in accordance with the dosage defined in the Summary of Product Characteristics	**1. Examinations and tests to determine eligibility** 1) white blood count; 2) red blood count; 3) haemoglobin level; 4) platelet count; 5) erythrocyte sedimentation rate; 6) alanine aminotransferase; 7) aspartate aminotransferase; 8) serum creatinine level; 9) C-reactive protein; 10) urinalysis; 11) tuberculin test or Quantiferon test; 12) HBs antigen; 13) anti-HCV antibodies; 14) HIV antigen (HIV Ag/Ab Combo); 15) serum electrolytes; 16) haematocrit; 17) chest X-ray; 18) ECG with its description; 19) endoscopic examination; 20) stool culture for bacteria and fungi; 21) stool examination for Clostridium difficile toxin. **2. Treatment monitoring** **2.1. Infliximab treatment monitoring** Within the framework of treatment monitoring, the medical service provider must perform the following examinations and tests not less frequently than at week 2, 6

azathioprine (AZA), (Mayo score > 6 in persons aged ≥ 18 years), or 2) intolerant to treatment with corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or 3) having contraindications to treatment with corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA). It is allowable to switch infliximab/vedolizumab if adverse effects occur or if the treatment is partially ineffective, which is defined as meeting one of the criteria listed in item 4. Ineffectiveness of standard treatment of a severe relapse of UC is defined as a failure of using 3–5 days of intravenous steroid therapy. Steroid-resistance means no clinical improvement despite using for 4 weeks a steroid at a daily prednisolone-equivalent dose of up to 0.75 mg/kg. Steroid-dependency means impossibility to reduce the prednisolone-equivalent dose of the steroid below 10 mg/day within 3 months of initiation of steroid treatment, or relapse of symptoms within 3 months of steroid discontinuation. Resistance (no adequate response) to immunosuppressive treatment means no remission or relapse of symptoms despite the use of immunosuppressive treatment for at least 3 months at adequate doses (azathioprine 2-2.5 mg/kg/day or 6-mercaptopurine at a dose of 1-1.5 mg/kg/day).		and 14 after the first dose of the drug: 1) evaluation of disease activity at weeks 2 and 6 after the first dose, on the partial Mayo scale or with the use of PUCAI, 2) evaluation of disease activity between weeks 6 and 14 after the first dose, on the full Mayo scale or with the use of PUCAI, 3) peripheral blood count, 4) CRP. Within the framework of maintenance treatment, the medical service provider must test the peripheral blood count, CRP, AlAT and AspAT, and must perform Mayo evaluation without endoscopy or PUCAI evaluation at least every 8 weeks. **2.2. Vedolizumab treatment monitoring** A. Within the framework of treatment monitoring, the medical service provider must perform the following examinations and tests not less frequently than at week 2, 6 and 14 after the first dose of the drug: B. 1) evaluation of disease activity at weeks 2 and 6 on the partial Mayo scale, C. 2) evaluation of effectiveness of the induction therapy at week 14 after the first dose, on the full Mayo scale, D. 3) peripheral blood count with differential count, E. 4) CRP. F. Within the framework of maintenance treatment, the medical service provider must test the peripheral blood count, CRP, AlAT and AspAT, and must perform

Treatment with ciclosporin is contraindicated in the following cases: 1) severe relapse of UC in the course of treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) or 2) hypomagnesaemia, or 3) potential drug-drug interactions, or 4) hyperkalaemia, or 5) hyperuricaemia, or 6) in patients above 80 years of age. Contraindications for ciclosporin treatment as per the SmPC: 1) renal impairment, 2) uncontrolled arterial hypertension, 3) hard-to-control infections, 4) malignancies. In the case of women of childbearing potential, it is necessary to obtain their consent for using birth control during the treatment and for up to 6 months after the last dose of vedolizumab. Also patients requiring continuation of treatment with infliximab/vedolizumab are found eligible for the programme, when their treatment with infliximab/vedolizumab up to date has been financed within the framework of hospitalisation based on Diagnosis-Related Groups (DRG), provided that: 1) they met the programme inclusion criteria before treatment initiation, 2) the total duration of therapy with infliximab/vedolizumab is not longer than the total duration of the induction and maintenance therapy defined below,		Mayo evaluation without endoscopy at least every 8 weeks. G. **3. Programme monitoring** 1) collecting in the patient's medical record the data on treatment monitoring and presenting those data each time at a request of the controllers of the National Health Fund (NFZ); 2) completing the data contained in the register (SMPT) available via the internet application made available by the Voivodeship Branch of the National Health Fund (OW NFZ), with the frequency consistent with the programme description and at the end of treatment; 3) transferring reporting-accounting information to the NFZ: the information is transferred to the NFZ in the paper or electronic form, in line with the requirements published by the National Health Fund.

3) the criteria constituting contraindications for participation in the programme are not met, 4) the circumstances referred to in the item concerning treatment termination do not exist when the patient's participation in the programme ends. **2. Criteria constituting contraindications for participation in the programme:** 1) hypersensitivity to the active substance or excipients; 2) severe viral, fungal or bacterial infections; 3) moderate to severe myocardial failure; 4) unstable coronary artery disease; 5) chronic respiratory failure; 6) chronic kidney failure; 7) chronic hepatic failure; 8) demyelinating syndrome or symptoms resembling this syndrome; 9) alcohol use disorder, alcohol induced liver injury or any active progressive hepatic disease; 10) pregnancy or breast-feeding; 11) diagnosis of precancerous conditions or malignancies, also in the period of 5 years preceding the time of determining eligibility for the programme; 12) complications that require a different therapeutic approach (e.g. surgical treatment). **3. Determination of the duration of treatment under the programme**		

1) induction therapy – infliximab/vedolizumab infusion at week 0, 2, 6; 2) maintenance treatment with infliximab/vedolizumab should be administered until no response to the treatment is found, but for not longer than 12 months in the case of infliximab and 54 weeks in the case of vedolizumab, from the time of administration of the first dose in induction therapy. The response is defined as a reduction in disease activity by at least 3 points on the Mayo scale or at least 20 points in PUCAI; **4. The treatment is terminated when** 1) the absence of treatment response defined as a reduction in disease activity by at least 3 points on the Mayo scale or at least 20 points in PUCAI is found, or 2) adverse effects of the treatment occur, or 3) complications requiring other specific treatment occur.		

TREATMENT OF CROHN'S DISEASE (CD) (ICD-10 K50)

SCOPE OF GUARANTEED MEDICAL SERVICE		
BENEFICIARIES	**CHART OF MEDICATION DOSAGE IN THE PROGRAMME**	**DIAGNOSTIC TESTS PERFORMED AS PART OF THE PROGRAMME**
i. Eligibility criteria for treatment under the programme. Patients who meet all the criteria listed in sections 1,2 or 1,3 are eligible for treatment with infliximab or adalimumab. Patients who meet all the criteria listed in sections 1 and 2 are eligible for treatment with vedolizumab. Patients who meet all the criteria listed in sections 1,2 and 4 are eligible for treatment with ustekinumab. 1) Age ≥6 years for infliximab or adalimumab therapy, or age ≥18 years for ustekinumab or vedolizumab therapy. 2) Severe active form of Crohn's disease (PCDAI score greater than or equal to 51 points for patients aged 6 years to 18 years inclusive, or CDAI score greater than 300 points for adults over 18 years) with no response to, or contraindications to, or symptoms of intolerance of treatment with glucocorticosteroids, immunosuppressive drugs or other TNF-alpha inhibitors. 3) Patients with Crohn's disease characterised by perinatal fistulas, who did not respond to primary treatment: antibiotics, immunosuppressive drugs,	**1. Dosage of infliximab.** Dosage of infliximab in accordance with the dosage defined in the Summary of Product Characteristics, taking into account the ECCO/ESPGHAN guidelines. **2. Dosage of adalimumab.** Dosage of adalimumab in accordance with the dosage defined in the Summary of Product Characteristics, taking into account the ECCO/ESPGHAN guidelines. **3. Dosage of ustekinumab.** Dosage of ustekinumab in accordance with the dosage defined in the Summary of Product Characteristics, taking into account the ECCO/ESPGHAN guidelines. **4. Dosage of vedolizumab.** Dosage of vedolizumab in accordance with the dosage defined in the Summary of Product Characteristics, taking into account the ECCO/ESPGHAN guidelines.	**1. Tests to determine eligibility for the treatment.** 1) complete blood count; 2) alanine aminotransferase (ALT); 3) aspartate aminotransferase (AST); 4) serum creatinine level; 5) C-reactive protein; 6) urinalysis; 7) tuberculin test or Quantiferon test; 8) HBs antigen; 9) anti-HCV antibodies; 10) HIV antigen (HIV Ag/Ab Combo); 11) serum electrolytes; 12) chest X-ray; 13) ECG with interpretation (required only in adults); 14) calculation of CDAI for patients over 18 years of age or PCDAI for children;

surgical treatment – regardless of the severity of the disease. 4) Documented lack of response to treatment with at least one other TNF-alpha inhibitor. 5) Also patients requiring continuation of treatment with infliximab or adalimumab, or vedolizumab, or ustekinumab are eligible for the programme, when their treatment with infliximab or adalimumab, or vedolizumab, or ustekinumab to date has been financed as part of hospitalisation based on Diagnosis-Related Groups (DRG) or as part of access to rescue therapy, provided that: – they met the programme inclusion criteria before treatment initiation, – the total duration of therapy with infliximab or adalimumab, or vedolizumab, or ustekinumab is not longer than the total duration of the induction and maintenance therapy defined below, – the criteria constituting contraindications for participation in the programme are not met, – the circumstances referred to in the item concerning treatment termination do not exist when the patient's participation in the programme ends. Women of childbearing potential must agree to use effective contraception during the treatment and		

– for up to 6 months after the last dose of infliximab, or – for up to 5 months after the last dose of adalimumab, or – for up to a minimum of 15 weeks after the last dose of ustekinumab, or – for up to at least 18 weeks after the last dose of vedolizumab. During the programme qualification process, all paediatric patients (children aged 6 years to 18 years inclusive) receive an Alert Card for patients receiving infliximab. Confirmation of receipt of this Alert Card by the patient is retained in the patient's medical records. **i. Maintenance treatment.** After the last dose in induction therapy, the response to treatment should be evaluated based on the PCDAI or CDAI score. Beneficiaries with clinical response are transferred to maintenance treatment. A clinical response is defined as a reduction in CDAI score of at least 70 points and at least 25% from baseline, or a reduction in PCDAI score of at least 15 points from baseline, or PCDAI ≤30 points. **i. Determination of the duration of treatment under the programme.** 1) Infliximab a. Induction therapy: 6 weeks b. Maintenance treatment with infliximab should be administered until loss of response, but not more than 24 months from the time of		

administration of the first dose in induction therapy. 2) Adalimumab a. Induction therapy: 12 weeks b. Maintenance treatment with adalimumab should be administered until loss of response (including the need to perform a surgical procedure for the disease), but not more than 12 months from the time of administration of the first dose of adalimumab in induction therapy. 3) Ustekinumab a. Induction therapy: 8 weeks b. Maintenance treatment with ustekinumab should be administered until loss of response, but not more than 12 months from the time of administration of the first dose of ustekinumab in induction therapy. 4) Vedolizumab a. Induction therapy: 14 weeks b. Maintenance treatment with vedolizumab should be administered until loss of response, but not more than 24 months from the time of administration of the first dose in induction therapy. **v. Programme exclusion criteria.** If at least one of the following criteria occurs, the patient is excluded from the program: 1) hypersensitivity to the drugs used in the programme;		

2) severe viral, fungal or bacterial infections; 3) moderate to severe myocardial failure; 4) unstable coronary artery disease; 5) chronic respiratory failure; 6) chronic kidney failure; 7) chronic hepatic failure; 8) demyelinating syndrome or symptoms resembling this syndrome; 9) alcohol use disorder, alcohol-induced liver injury or any active progressive hepatic disease; 10) pregnancy or breast-feeding; 11) diagnosis of precancerous conditions or malignancies in the period of 5 years preceding the time of determining eligibility for the programme; 12) complications requiring change in management (e.g. radical surgical treatment – surgical repair of fistulas can and should take place as clinically indicated during biological treatment). **v. End of treatment in the programme.** The treatment should be discontinued when at least one of the criteria set out in items 1 to 3 is met. 1) Lack of treatment effects 2) Adverse effects of the treatment 3) Complications requiring other specific treatment		

A clinical response is defined as a reduction in CDAI score of at least 70 points and at least 25% from baseline, or a reduction in PCDAI score of at least 15 points from baseline, or PCDAI ≤30 points. The available data do not justify further treatment with infliximab in children and adolescents who have not responded within the first 10 weeks of treatment, or further treatment with vedolizumab in those who have not responded within the first 14 weeks of treatment. 4) In case of intolerance of the started treatment with infliximab or adalimumab, or ustekinumab, or vedolizumab, or in case of adverse events preventing its continuation, another anti-TNF drug may be used, authorised in a Crohn's disease treatment programme, if the patient meets the eligibility criteria for that programme, unless it was used earlier. 5) In the event of another exacerbation in an adult patient (over 18 years of age) after the end of adalimumab treatment within the drug programme, a medically justifiable re-enrollment in the programme is possible, not earlier, however, than 8 weeks after the end of the previous therapy. 6) In the event of another exacerbation in an adult patient (over 18 years of age) after the end of infliximab or ustekinumab, or vedolizumab treatment within the drug programme, a medically justifiable re-enrollment in the programme is possible, not		

earlier, however, than 16 weeks after the end of the previous therapy.		

Summary of changes

Protocol version	~~1.1~~2.0
STUDY SUMMARY	1.1 **Subject Population:** Consecutive IBD (UC or CD) adult (aged ≥18) outpatients attending the gastroenterology clinics in Poland scheduled for vedolizumab infusion in the scope of Drug Program between Sep 2020 – Mar 2022.
	2.0 **Subject Population:** Consecutive IBD (UC or CD) adult (aged ≥18) outpatients attending the gastroenterology clinics in Poland scheduled for vedolizumab infusion in the scope of Drug Program between Sep 2020 – Mar 2022 **for UC patients and between Sep 2020 and Jul 2022 for CD patients.**
	1.1 **Number of Subjects:** All adult patients qualified to CD or UC Drug Program between Sep 2020 and Mar 2022.
	2.0 **Number of Subjects:** All adult patients qualified to CD or UC Drug Program between Sep 2020 and Mar 2022 **for UC patients and between Sep 2020 and Jul 2022 for CD patients.**

	1.1 **Duration of Study:** Overall Study Duration: 25 months Enrolment period: 19 months Treatment/Follow-up: 3.5 months (14 weeks)
	2.0 **Duration of Study:** Overall Study Duration: **29 months** Enrolment period: **19 months for UC patients, 23 months for CD patients** Treatment/Follow-up: 3.5 months (14 weeks)
2 Introduction	1.1 Having in regards that recruitment period in KUJAWIAK study is 19 months it is expected that total study population will be approximately 300 patients, including UC and CD patients.
	2.0 Having in regards that recruitment period in KUJAWIAK study is 19 months **for UC patients and 23 months for CD patients** it is expected that total study population will be approximately 300 patients, including UC and CD patients.
6 Study Design and Plan	1.1 Prospective, observational (non-interventional), multicentre study with consecutive patients aged ≥ 18 enrolled between Sep 2020 and Mar 2022 with ulcerative colitis or Crohn's disease fulfilling inclusion criteria to Drug Program.
	2.0 Prospective, observational (non-interventional), multicentre study with consecutive patients aged ≥ 18 enrolled between Sep 2020 and Mar 2022 **with ulcerative colitis or between Sep 2020 and Jul 2022 with Crohn's disease** fulfilling inclusion criteria to Drug Program.
6.1 Study Schedule	1.1 Planned Start of Study: Sep 2020 Planned collection of first data point: Sep 2020 Planned End of Study: Sep 2022 Planned collection of the last data point: Sep 2022 Planned completion of the Study Report: Dec 2022

	2.0 Planned Start of Study: Sep 2020 Planned collection of first data point: Sep 2020 Planned End of Study: **Jan 2023** Planned collection of the last data point: **Jan 2023** Planned completion of the Study Report: **Apr 2023**
9.1 Statistical Analysis Plana	1.1 This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data (listed in 6.6 and Appendix 1 Data collection overview), except variables collected only for the purpose of data cleaning.
	2.0 This study is observational and epidemiological methods will be employed for data analyses. Descriptive analysis will be performed of all collected data (listed in 6.6 and Appendix 1 Data collection overview), except variables collected only for the purpose of data cleaning. **All analyses will be performed separately for UC and CD patients.**
9.3 Determination of Sample Size	1.1 No predefined sample size has been assumed for this study, and all data collected during KUJAWIAK study will be considered for analytical purposes. Nevertheless, a potential for enrolment during recruitment period indicates that approximately 300 consecutive patients fulfilling inclusion criteria and not meeting exclusion criteria will be recruited and observed.
	2.0 No predefined sample size has been assumed for this study, and all data collected during KUJAWIAK study will be considered for analytical purposes. Nevertheless, a potential for enrolment during recruitment period indicates that approximately 300 consecutive patients, **including both UC and CD,** fulfilling inclusion criteria and not meeting exclusion criteria will be recruited and observed.
Appendices	Updated Summary of changes