STUDY PROTOCOL

KIC-START: A LOW-INTERVENTIONAL, PROSPECTIVE, MULTI-CENTER STUDY TO EVALUATE REAL-WORLD CLINICAL, BIOCHEMICAL AND PATIENT-REPORTED RESPONSES TO TOFACITINIB INDUCTION THERAPY IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS IN SWITZERLAND

Compound Number:	CP-690550
Compound Name:	Tofacitinib (Xeljanz®)
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Short Title: A Low-Interventional Study To Evaluate Clinical, Biochemical, And Patient-Reported Responses To Tofacitinib Induction Therapy For Ulcerative Colitis

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	23 July 2021	NA
Protocol Amendment 1 substantial	29 September 2021	Summary and Section 9.3: Added, "The Clinical Trial Unit of Inselspital is responsible for study data management activities (implementation and maintenance of the study database)". Section 1.3 – Table 1 Clarification that informed consent is only required once during screening visit. Section 1.3 – Table 1; Section 3.1 – Table 4 and Section 8.1.1.3 To comply with the request of ethic committee instead of date of birth, only month and year of birth will be collected. Section 4.2.1; Section 5.2 and section 7.1 To address ethics committee comments and stay in line with drug label pregnancy was eliminated as a reason for study exclusion and discontinuation. Section 5.1 Clarification in inclusion criteria section that decision to prescribe tofacitinib is independent of study participation. Appendix 5 Clarification of study and patient data location. Harmonization of PRO names throughout the document. Minor administrative changes/clarifications and corrections throughout the document.

Protocol Amendment 2 administrative	22 March 2022	Cover page Removed SNCTP Number as not applicable. Sections 8.3.10 and 8.4 To align with the safety language in the new Pfizer LIS2 protocol template (CT45-GSOP-RF15B 2.0), as well as comply with the nature and design of the study, the language about medication errors and overdose was updated. Specifically, removed superfluous text in section 8.3.10, removed information on what should be done in the event of an overdose was and replaced it with a reference to section 8.3.10. Medication Errors. Definitions for medication error and overdose were added to Appendix 2 (sections 10.2.3 and 10.2.4). Appendix 1 Added contact details for medical monitor to Responsible Parties list (Section 10.1.2) and updated Pfizer Team details to reflect any changes in positions. Section 8.3 and Appendix 1 section 10.2.2 Removed the contact details for the Pfizer clinician and medical monitor from the footnotes, as these are provided in the Responsible Parties list (Section 10.1.2). Table 7 removed from protocol and put in a separate sites and investigators log, so that protocol does not need to be amended every time a site and/or investigator is added or removed from the study.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title

A low-interventional study to evaluate clinical, biochemical, and patient-reported responses to tofacitinib induction therapy for ulcerative colitis

Rationale

A number of studies have been published demonstrating the RWE of tofacitinib in patients with UC.[1-8] While it is known that tofacitinib therapy is associated with a rapid onset of symptom relief in terms of the PMS components (stool frequency and rectal bleeding), the response of other important PROs, such as fatigue, urgency and abdominal pain, are less well characterized.[9,10] Measuring these PROs will provide a broader understanding of how patients experience response to tofacitinib treatment. Moreover, response of fCAL during tofacitinib induction therapy is currently not fully understood.[11] Regular measurements of fCAL levels, a widely used biomarker in UC, will provide a measure of the response of intestinal inflammation to tofacitinib induction therapy. Early measurements will assess the validity of fCAL as an early biochemical predictor of treatment response.

This study aims to generate granular RWD on and provide the opportunity to explore the relationships between tofacitinib induction therapy and changes in PMS, PROs and intestinal inflammation during tofacitinib induction therapy in UC.

Objectives and Endpoints

Primary Objective:	Primary Endpoint:
Evaluate the RW effectiveness of tofacitinib induction therapy in patients with UC.	Proportion of participants achieving clinical response[a] at W8.
Secondary Objectives:	**Secondary Endpoints:**
Evaluate RW response to tofacitinib treatment based on PMS.	• Proportion of participants achieving clinical remission[b] at W8. • Proportion of participants achieving clinical response[a] at W16. • Proportion of participants achieving clinical remission[b] at W16.
Evaluate the RW response to tofacitinib treatment on quality of life based on IBDQ score.	• Proportion of participants achieving IBDQ remission[c] at W8. • Proportion of participants achieving IBDQ remission[c] at W16. • Proportion of participants achieving IBDQ response[d] at W8. • Proportion of participants achieving IBDQ response[d] at W16.
Evaluate RW response to tofacitinib treatment based on fCAL concentrations.	• Proportion of participants achieving biochemical remission[e] at W8. • Proportion of participants achieving biochemical remission[e] at W16.
Elucidate fCAL and PRO responses to tofacitinib induction therapy for UC.	Median changes from baseline in PROs and fCAL over time (ie, map response curves).
Assess whether PRO responses occur prior to, with or lag behind clinical responses.	Correlations between changes in amplitude and timing of PMS, PROs, IBDQ score and fCAL concentrations.
Verify the validity of fCAL as a convenient surrogate biomarker to assess early response to tofacitinib treatment.	• Median fCAL concentrations over time stratified by W8 and W16 clinical remission status.[b] • Median fCAL concentrations over time stratified by W8 and W16 clinical response status.[a] • Median fCAL concentrations at W8 by W8 clinical response status.[a]
Exploratory Objectives:	**Exploratory Endpoints:**
Assess effect of prior exposure to biologics, concomitant medications and tofacitinib induction dose, on treatment outcomes.	Stratification of PMS outcomes, PROs and fCAL levels based on: i) prior exposure to TNFi, vedolizumab and ustekinumab; ii) concomitant medication with corticosteroids or aminosalicylic acids; iii) predominant tofacitinib dose.
Assess effect of baseline patient demographics and disease characteristics on the likelihood of achieving clinical, fCAL or PROs response.	Regression analyses on baseline patient and disease characteristics with respect to PMS, fCAL or PROs measures.

Evaluate RW response to tofacitinib treatment based on FMS and IUS outcomes.	• Proportion of participants achieving FMS response[f] at W8. • Proportion of participants achieving remission[g] at W8. • Proportion of participants achieving FMS response[f] at W16. • Proportion of participants achieving remission[g] at W16. • Proportion of participants achieving mucosal healing[h] at W8. • Proportion of participants achieving mucosal healing[h] at W16. • Proportion of participants achieving response according to IUS assessment[i] at W8. • Proportion of participants achieving remission according to IUS assessment[i] at W8. • Proportion of participants achieving response according to IUS assessment[i] at W16. • Proportion of participants achieving remission according to IUS assessment[i] at W16.
Evaluate impact of tofacitinib treatment on activity of individual EIMs and categories of EIMs (mucocutaneous, musculoskeletal, ocular, hepatobiliary).	• Proportion of participants with improvement in EIM[j] (individual or categorical) at W8. • Proportion of participants with improvement in EIM[j] (individual or categorical) at W16.

a. Clinical response: reduction in PMS from baseline of ≥2 points or achieving clinical remission.[12]
b. Clinical remission: PMS of ≤2 with no subscore >1.[12]
c. IBDQ remission: IBDQ score ≥170.[12]
d. IBDQ response: IBDQ score ≥16 points higher than IBDQ baseline score.
e. Biochemical remission: fCAL concentration ≤250 mg/g.[11] Optimal fCAL cut-off values for the detection of active disease vary from 50 µg/g to 250 µg/g [2, 38, 47] depending on the test used, location of the disease and intra-individual patient variability. In this study, biochemical remission is defined as a fCAL concentration ≤250 µg/g.
f. FMS response: decrease from baseline total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥1 or absolute rectal bleeding subscore ≤1.[12]
g. Remission: a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0.[12]
h. Mucosal healing: a Mayo endoscopic subscore of ≤1.[12]
i. According to treating physician's assessment of bowel wall thickness, normalization and extension; bowel wall vascularity, loss of stratification, loss of colonic haustration, structure formation and hyperechogenic reaction adjacent to the bowel wall.
j. According to treating physician's observations and assessments.

Overall Design

This study is an open-label, prospective, low-interventional, multi-center study conducted in Switzerland in a real-world setting uncontrolled by any comparison groups. Patients will be included if they are 18 years of age or older, provide written, informed consent and are prescribed tofacitinib for moderate to severe UC as per the Swiss label and as per physician's clinical judgement, independently of this study.[13] Importantly, no additional endoscopy will be performed and data will only be used from endoscopies and intestinal ultrasound assessments performed as SOC and at physician's discretion.

A research version of the Sidekick Health IBD companion App, designed for the study, will be used to conveniently collect PROs at predefined timepoints according to the study protocol. Via their personal mobile phone, participants will be provided with brief PRO questionnaires that encompass important elements of the subjective experience of UC. PROs will be collected daily until Week 2 and thereafter twice weekly until Week 8. To fully capture the 16-week induction period and account for delayed responders, PROs will be recorded in all participants at Week 16. Patients not owning a mobile phone compatible with the Sidekick Health IBD App or not willing to have it installed will not be included in the study.

For regular and convenient fCAL measurements, participants will use the CALEX® Cap system (BÜHLMANN Laboratories AG), to collect stool samples at home. Samples will be analyzed with the Quantum Blue® (BÜHLMANN Laboratories AG) device at POC to quantitatively assess fCAL concentration. To allow valuable insights into the sensitivity and timing of early fCAL responses with respect to disease activity and symptom changes during induction therapy, fCAL concentrations will be measured more often during the first week of induction therapy (4 times), followed by measurements on a weekly basis during the following weeks and up to Week 8. An additional measurement is planned at Week 16.

Number of Participants

Approximately 60 participants will be enrolled. A participant is considered enrolled if protocol-required procedures at baseline visit are performed. An enrolled participant who discontinues the study before Week 8 study (ie, Week 8 visit is not performed), will be replaced by enrolling a new participant. Participants who are screened for the purpose of determining eligibility for the study, but do not meet the eligibility criteria, or who do not perform the baseline visit, are not considered enrolled to the study and are declared screen failures. Screen failures will not be rescreened.

Treatment Cohorts and Duration of Study Participation

Patients who are prescribed tofacitinib (Xeljanz®) for the treatment of moderately to severely active UC will be included in the study. This protocol does not recommend or promote the prescription and use of tofacitinib, and tofacitinib will not be provided as part of this study. The clinical decision for the prescription of tofacitinib should be clearly separated from the decision to propose enrollment in this study to the patient. It is expected that a large proportion of enrolled participants will have prior exposure to TNF-antagonists, as tofacitinib is commonly prescribed in this population in Switzerland.

Doses of tofacitinib treatment should be based on the Swiss label recommendations,[13] as well as clinical and individual needs, and are determined by the treating physician. The standard tofacitinib induction dosing is 10 mg twice daily for an 8-week induction period, after which the dosage is reduced to the recommended maintenance dose of 5 mg twice daily, although prolongation of the 10 mg twice daily dose up to 16 weeks is permitted if clinically indicated. If off-label doses are used, inclusion in the study is permitted.

The active study period starts at patient signature of ICD, obtained not later than the first day of tofacitinib treatment initiation and continues for the entire 8-week induction period, and additionally at Week 16. Data collected up to 42 days prior to the first day of tofacitinib initiation (ie, baseline visit) can be used for study purposes and analyses. The safety reporting period will extend for an additional 4 weeks (28 days) after the Week 16 visit, or after the discontinuation/withdrawal date, if the participant has discontinued the study prematurely.

A participant is considered to have completed the study if he/she has completed all study procedures, including the Week 16 study visit and the 28 days of safety monitoring following this visit.

Data Monitoring Committee or Other Independent Oversight Committee:

Not used in this study.

Statistical Methods

This study seeks to test the following hypotheses:

- Tofacitinib induction therapy is associated with a rapid improvement in the PMS, intestinal inflammation (ie, reduced fCAL concentrations), QoL and symptoms (PROs).
- Changes in different types of treatment outcomes (ie, PMS, PROs and fCAL concentrations) are correlated.
- Improvements in PROs and fCAL concentrations can predict treatment outcomes (ie, clinical outcome measures) at end of induction therapy.

Based on PMS data from the OCTAVE Induction and RW studies, feedback from Swiss gastroenterologists on drop-out rates during the first 8 weeks of tofacitinib therapy and assuming that most participants will have prior exposure to TNF-antagonists, we estimated that a sample size of 60 participants should be sufficient to detect a significant reduction from baseline in PMS at Week 8.

Data analysis will include both ITT and PP analyses. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP.

For data management, the EDC system SecuTrial will be used. All data entered in the EDC system will be transferred to the database using TLS encryption and will be stored on a Linux server in a dedicated Oracle database at the Inselspital Bern, Switzerland. The Clinical Trial Unit of Inselspital is responsible for study data management activities (implementation and maintenance of the study database). Participants' study-related data will be collected in a coded manner. No interim analyses are planned. At final analysis, data files will be extracted from the database into statistical packages to be analyzed.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to STUDY ASSESSMENTS AND PROCEDURES (Section 8) of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unscheduled visits) in addition to those listed in the SoA table, to conduct evaluations or assessments required to protect the well-being of the participant. Such visits should be documented in the study specific form "Unscheduled visit", detailing the reason for the unscheduled visit, clinical and other procedures performed and outcomes, where applicable.

Table 1. SoA

Visit Identifier Abbreviations used in this table may be found in Appendix 6.	Screening[a] Day -35 to -7	Baseline[b] Day 0	Visit Week 8 Day 56	Visit Week 16 Day 112	Follow-up[c] Week 20 Day 140	Early Termination/ Discontinuation[d]
Visit Window	**±7 days**		**±14 days**	**±14 days**	**+7 days**	
Protocol-required assessments						
Eligibility criteria assessment	X					
Informed consent	X					
Patient demographics: month and year of birth, gender, BMI, smoking status		X				
UC disease characteristics						
PMS		X	X	X		X
Advanced treatment history		X				
Co-morbidities, including EIMs		X	X	X		
Study Registration		X				
Introduction to Sidekick Health IBD App and stool home-collection kit		X				
Tofacitinib exposure (dose)		X	X	X		X
Concomitant treatment(s)		X	→	→	→	X
Serious and nonserious AE monitoring	X	→	→	→	→	→
SOC assessments						
UC disease characteristics						
Date of UC diagnosis		X				
UC extent (location)[e]	X	X	X	X		
CRP level	X	X	X	X		
Mayo Endoscopic subscore[f]	X	X	X	X		
IUS[g]	X	X	X	X		

Abbreviations: → = ongoing/continuous procedure.

a. Performing screening and baseline visit on the same day is permitted. Participant should however be given sufficient and reasonable time to consider participation in the study (ICD can be provided prior to screening visit).

b. Baseline is defined as day of tofacitinib first dose intake. In case the participant starts tofacitinib later than day of baseline visit, PROs and stool collection should begin with tofacitinib first dose intake.

c. A follow-up contact with participant must be scheduled at the end of the AE/SAE active collection period as defined in Section 8.3.1. Safety monitoring will generally continue for an additional 4 weeks (28 days) after Week 16 visit, or after the discontinuation/withdrawal date for participants who discontinue the study prematurely.

d. Study-specific discontinuation form will be used to collect reason for study or drug discontinuation, clinical and other undertaken procedures at discontinuation, as well as outcome, where applicable.

e. Extent of disease is defined based on endoscopic findings. Endoscopy is not mandatory. Disease extent will only be assessed if endoscopy is performed as part of SOC. Endoscopy is expected at either screening/baseline visit and again at either Week 8 or Week 16 visits.

f. Mayo Endoscopic subscore is based on endoscopic findings. Mayo Endoscopic subscore and PMS will be used to calculate FMS. FMS will only be calculated if endoscopy is performed as part of SOC and according to physician's assessment. Endoscopy is expected at either screening/baseline visit and again at either Week 8 or Week 16 visits.

g. Data from IUS will be collected and analyzed in an exploratory fashion, only if available and performed as part of SOC.

Other procedures between study visits:

PROs and fCAL levels will be regularly assessed between scheduled study visits. Table 2 summarizes the frequency of these assessments during the study period. Refer to STUDY ASSESSMENTS AND PROCEDURES section (Section 8) of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Table 2. Schedule of Procedures Between Study Visits

		week 1							week 2							week 3							week 4							week 5							week 6							week 7							week 8							...	week 16
	Days from baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56		112
Stool sample collection* for fCAL analysis		■		■		■		■							■							■							■							■							■							■							■			■
PROs collection	Stool frequency	■	■	■	■	■	■	■	■	■	■	■	■	■	■			■				■			■				■			■				■			■				■			■				■			■			■		■
	Rectal bleeding	■	■	■	■	■	■	■	■	■	■	■	■	■	■			■				■			■				■			■				■			■				■			■				■			■			■		■
	Urgency of defecation	■	■	■	■	■	■	■	■	■	■	■	■	■	■			■				■			■				■			■				■			■				■			■				■			■			■		■
	Abdominal pain	■	■	■	■	■	■	■	■	■	■	■	■	■	■			■				■			■				■			■				■			■				■			■				■			■			■		■
	Quality of sleep	■	■	■	■	■	■	■	■	■	■	■	■	■	■			■				■			■				■			■				■			■				■			■				■			■			■		■
	Daily fatigue	■	■	■	■	■	■	■	■	■	■	■	■	■	■			■				■			■				■			■				■			■				■			■				■			■			■		■
	Weekly fatigue	■						■							■							■							■							■							■							■							■		■
	Disease-specific quality of life	■													■							■							■							■							■							■							■		■

** Stool samples can be collected at +/- 3 days starting from week 2.*

2. INTRODUCTION

This low-interventional study will evaluate the effectiveness of tofacitinib (Xeljanz®) in treating patients with moderately to severely active UC, by collecting prospective longitudinal data on PMS, PROs and fCAL levels in a real-world setting in Switzerland. Tofacitinib is an oral JAKi that is approved for the treatment of moderately to severely active UC and will be studied in participants with UC. Tofacitinib will be prescribed according to the approved Swiss product label[13] and treatment will be guided by clinical judgement of study investigators, independently of this study. This protocol does not recommend or promote the prescription and use of tofacitinib, and tofacitinib will not be provided as part of this study. The clinical decision for the prescription of tofacitinib should be clearly separated from the decision to propose enrollment in the study to the patient.

This study is expected to contribute to the growing body of RWE of tofacitinib's safety and efficacy profile in UC. Conventional clinical outcomes will give a better understanding of response and remission rates in a representative, post-marketing population. These conventional measures will be supplemented by an array of PROs to give a broader understanding of how patients experience response to treatment. Regular measurement of fCAL levels, a widely used biomarker in UC utilized to guide treatment decisions, which shows potential as an early biochemical predictor of treatment response, will provide a measure of the response of intestinal inflammation to tofacitinib induction therapy.

2.1. Study Rationale

A number of studies have now been published demonstrating the RWE of tofacitinib in patients with UC, however these studies did not assess PROs beyond the rectal bleeding and stool frequency components of the Mayo score.[1-8] Moreover, while it is known that tofacitinib therapy is associated with a rapid onset of symptom relief in terms of the PMS components (stool frequency and rectal bleeding), the response of other important PROs, such as fatigue, urgency and abdominal pain, are less well characterized.[9,10] Measuring these PROs will provide a broader understanding of how patients experience response to tofacitinib treatment.

To address this gap and to supplement data from clinical trials, this study aims to generate granular RWD on and provide the opportunity to explore the relationships between tofacitinib induction therapy and changes in PMS, PROs and intestinal inflammation during tofacitinib induction therapy. Furthermore, it will allow us to gain insight into time to symptom relief in a real-world setting, which has hitherto not been studied.

2.2. Background

Ulcerative colitis is a chronic inflammatory disease that causes inflammation and ulceration of the colon and rectum and is characterized by a remitting and relapsing clinical course. Together with CD, it is a major component of the term IBD. Symptoms are often unspecific and may vary with disease activity and can include debilitating episodes of rectal bleeding, urgency, diarrhea and abdominal pain, potentially causing a life-long burden and reduction of quality of life for patients.[14-16] Endoscopy is the fundamental diagnostic tool used for initial

diagnosis of UC, to distinguish between CD and UC, monitor disease and assess and treat complications. Although endoscopy has long been used, technologic advances have allowed additional tools to assist in the management of IBD. In Switzerland, IUS is commonly used in daily practice and represents a non-invasive, well-tolerated and cost-effective modality to assess disease activity and to guide therapy decisions in patients with UC.[17]

Data from the Swiss IBD cohort study suggests that the overall incidence and prevalence of IBD in Switzerland is increasing. IBD has recently been recognized as a global chronic condition, with a prevalence of approximately 5 million people diagnosed with IBD worldwide. The last decade has brought significant progress in our understanding of the pathophysiology of IBD, with several effective treatments targeting the autoinflammatory pathways that mediate the disease.[18]

The efficacy and safety of tofacitinib for the treatment of moderately to severely active UC has been well characterized in pivotal clinical trials.[12] Tofacitinib is taken as a 10 mg twice daily dose for an 8-week induction period, after which the dosage is reduced to the recommended maintenance dose of 5 mg twice daily, although prolongation of the 10 mg twice daily induction dose up to 16 weeks is permitted if clinically indicated.[13] If adequate therapeutic benefit is not achieved after 16 weeks of 10 mg twice daily dosing, tofacitinib must be discontinued.

Understanding the effect of therapies on different PROs is increasingly recognized as a crucial aspect in the successful management of IBD patients.[9,10,19] While the widely used and validated Mayo score in UC includes patient-reported stool frequency and rectal bleeding, the response of other important PROs, such as fatigue, mood, appetite and pain, are less well -characterized. Measuring these holistic PROs can provide insight into aspects of the disease and the benefits of a given therapy that are not fully captured by the clinical endpoints used in research and clinical practice. The importance of capturing PROs is further evidenced by the emergence of guidance from regulatory authorities,[20-29] which can rapidly be turned into insights that enable physicians to optimize disease management and deliver tailored care to their patients. In addition, embedding digital patient solutions in clinical care may be valuable in IBD management and this study will assess the use of a research version of the IBD companion App, developed by Sidekick Health (Sidekick Health IBD App) specifically for the study, for the collection of early and holistic PROs. The native (non-research) Sidekick Health IBD App is already available to IBD patients in Switzerland through the Swiss IBD patient association (Crohn Colitis Schweiz). At their own discretion, study participants will have the opportunity to use functionalities of the native Sidekick Health IBD App (eg, disease-specific and lifestyle management modules, activity tracking, food diary), in addition to completing the research program.

Increased understanding of IBD pathophysiology has led to the development of disease biomarkers to gauge response to treatment, of which fCAL is among the most well-established.[30-32] fCAL is a small anti-microbial protein detected in stool that constitutes approximately 60% of neutrophil cytoplasm. As migration of neutrophils into the intestinal mucosa is a hallmark of active intestinal inflammation, fCAL serves as a sensitive

noninvasive marker to differentiate IBD from IBS, measure response to therapy and to monitor and predict disease flares.[33-36] In addition, fCAL is extremely resistant to bacterial degradation, being stable in stool for up to one week at room temperature, which contributes to its suitability as a laboratory marker. To date, the gold standard test to assess fCAL levels in IBD patients is ELISA. This method has been used for over 20 years, but it requires specialized expertise and laboratory equipment, is time-consuming and is costly. The BÜHLMANN Quantum Blue® point-of-care device used in this study, offers an alternative method to the standard ELISA technique, which is easy to use, affordable and provides accurate results within 15 minutes.

In Switzerland, monitoring fCAL levels has been incorporated into best-practice recommendations for monitoring IBD disease activity,[37,38] and reimbursement of fCAL analyses by the compulsory Swiss health care insurance is stipulated by the Swiss FOPH.

2.2.1. Clinical Overview

Three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with UC were conducted to evaluate the efficacy of tofacitinib as induction (OCTAVE Induction 1 and 2) and maintenance therapy (OCTAVE Sustain trial).[12] In the OCTAVE Induction 1 and 2 trials, participants were randomized to receive therapy with 10 mg twice daily tofacitinib therapy or placebo for 8 weeks. The primary end point was remission at 8 weeks, defined as a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0. In the OCTAVE Sustain trial, participants who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. The primary end point was remission at 52 weeks.

A post-hoc analysis of data from the 2 phase 3 OCTAVE Induction 1 and 2 clinical trials demonstrated significant and rapid-onset (within 3 days) of improvement in symptoms, in terms of components of the Mayo score (stool frequency, rectal bleeding) among participants given tofacitinib compared to placebo. Daily Mayo stool frequency and rectal bleeding subscores were calculated using diary data from the first 15 days of therapy.[39] Little is known however about how quickly physicians and patients should expect to see other relevant symptoms, such as fatigue and urgency, decrease following commencement of tofacitinib therapy. It is specifically unclear whether these PRO responses occur prior to, with or lag behind clinical responses.

In both OCTAVE induction trials, the proportion of participants with an IBDQ score indicative of remission (a score of ≥170) and the proportion of participants with an IBDQ score indicative of a treatment response (a score ≥16 points higher than the baseline score) were significantly larger with tofacitinib than with placebo at weeks 4 and 8.

In terms of safety, in the OCTAVE Induction 1 and 2 trials, the rates of overall infection and serious infection were higher with tofacitinib than with placebo.

Despite fCAL being one of the few reliable and widely employed biomarkers for disease activity and treatment response in IBD, the response of fCAL during tofacitinib induction therapy for UC is currently not fully understood. In a double-blind, placebo-controlled, phase 2 trial, correlations between clinical and endoscopic outcomes with fCAL concentrations were assessed at Week 8. Only limited data are available, but a moderate correlation of fCAL with tofacitinib-induced clinical improvement was observed.[11]

2.3. Benefit/Risk Assessment

In this study, measures are taken to minimize risks to participants and are justified by the anticipated benefits that may be afforded to participants.

Participants are given the opportunity to report symptoms regularly and are provided throughout the study with interactive IBD-specific educational and lifestyle modules through the Sidekick Health IBD App. Regularly reporting and learning about symptoms can provide stimulus for the participant to build necessary confidence to handle symptoms and self-management of their disease. On the other hand, repeatedly focusing on disease symptoms may promote a disease-centered attitude and negatively impact the participant's perception of the efficacy of their treatment.

Short and simple validated questionnaires have been chosen to assess PROs that are regularly collected, such as to reduce participant questionnaire burden but still maintain the validity and utility of the assessments.[27]

Stool sample collection for fCAL measurements is designed in this study such as to minimize burden to participants. The method used for sample collection is noninvasive, rapid, easy to use and will be carried out at the participant's residence. Eleven samples will be collected over an 8-week period (56 days), and once again at Week 16. As fCAL is a widely used biomarker in gastroenterologists' clinical practice in Switzerland, UC patients are used to performing stool sample collection. Thus, we presume that the stool sample collections will not impose excessive burden, nor discomfort, on the study participants.

Lastly, this study is categorized as Category A research project according to the Swiss Human Research Ordinance as the planned measures for sampling biological material (stool collection) and collection of personal data and PROs through questionnaires entail only minimal risks and burdens in terms of intensity and potential risk on participant's health. Treating physicians and site staff will be blinded to their patient's fCAL measurements and PRO responses, thus these additional measurements will not be used to inform treatment decisions. Moreover, tofacitinib will be prescribed in accordance with the approved Swiss product label for the approved indication and population.

Full information about the known and expected benefits and risks and reasonably expected AEs of tofacitinib (Xeljanz®) may be found in the approved Swiss product label, which is the SRSD for this study. The SRSD should be used by the investigator for prescribing purposes and guidance.

3. RESEARCH QUESTIONS, OBJECTIVES AND ENDPOINTS

Table 3. Study Objectives and Endpoints

Primary Objective:	**Primary Endpoint:**
Evaluate the RW effectiveness of tofacitinib induction therapy in patients with UC.	Proportion of participants achieving clinical response[a] at W8.
Secondary Objectives:	**Secondary Endpoints:**
Evaluate RW response to tofacitinib treatment based on PMS.	• Proportion of participants achieving clinical remission[b] at W8. • Proportion of participants achieving clinical response[a] at W16. • Proportion of participants achieving clinical remission[b] at W16.
Evaluate the RW response to tofacitinib treatment on quality of life based on IBDQ score.	• Proportion of participants achieving IBDQ remission[c] at W8. • Proportion of participants achieving IBDQ remission[c] at W16. • Proportion of participants achieving IBDQ response[d] at W8. • Proportion of participants achieving IBDQ response[d] at W16.
Evaluate RW response to tofacitinib treatment based on fCAL concentrations.	• Proportion of participants achieving biochemical remission[e] at W8. • Proportion of participants achieving biochemical remission[e] at W16.
Elucidate fCAL and PRO responses to tofacitinib induction therapy for UC.	Median changes from baseline in PROs and fCAL over time (ie, map response curves).
Assess whether PRO responses occur prior to, with or lag behind clinical responses.	Correlations between changes in amplitude and timing of PMS, PROs, IBDQ score and fCAL concentrations.
Verify the validity of fCAL as a convenient surrogate biomarker to assess early response to tofacitinib treatment.	• Median fCAL concentrations over time stratified by W8 and W16 clinical remission status.[b] • Median fCAL concentrations over time stratified by W8 and W16 clinical response status.[a] • Median fCAL concentrations at W8 by W8 clinical response status.[a]
Exploratory Objectives:	**Exploratory Endpoints:**
Assess effect of prior exposure to biologics, concomitant medications and tofacitinib induction dose, on treatment outcomes.	Stratification of PMS outcomes, PROs and fCAL levels based on: i) prior exposure to TNFi, vedolizumab and ustekinumab; ii) concomitant medication with corticosteroids or aminosalicylic acids; iii) predominant tofacitinib dose.
Assess effect of baseline patient demographics and disease characteristics on the likelihood of achieving	Regression analyses on baseline patient and disease characteristics with respect to PMS, fCAL or PROs

clinical, fCAL or PROs response.	measures.
Evaluate RW response to tofacitinib treatment based on FMS and IUS outcomes.	• Proportion of participants achieving FMS response[f] at W8. • Proportion of participants achieving remission[g] at W8. • Proportion of participants achieving FMS response[f] at W16. • Proportion of participants achieving remission[g] at W16. • Proportion of participants achieving mucosal healing[h] at W8. • Proportion of participants achieving mucosal healing[h] at W16. • Proportion of participants achieving response according to IUS assessment[i] at W8. • Proportion of participants achieving remission according to IUS assessment[i] at W8. • Proportion of participants achieving response according to IUS assessment[i] at W16. • Proportion of participants achieving remission according to IUS assessment[i] at W16.
Evaluate impact of tofacitinib treatment on activity of individual EIMs and categories of EIMs (mucocutaneous, musculoskeletal, ocular, hepatobiliary).	• Proportion of participants with improvement in EIM[j] (individual or categorical) at W8. • Proportion of participants with improvement in EIM[j] (individual or categorical) at W16.

a. Clinical response: reduction in PMS from baseline of ≥2 points or achieving clinical remission.[12]
b. Clinical remission: PMS of ≤2 with no subscore >1.[12]
c. IBDQ remission: IBDQ score ≥170.[12]
d. IBDQ response: IBDQ score ≥16 points higher than IBDQ baseline score.
e. Biochemical remission: fCAL concentration ≤250 mg/g.[11] Optimal fCAL cut-off values for the detection of active disease vary from 50 µg/g to 250 µg/g [2, 38, 47] depending on the test used, location of the disease and intra-individual patient variability. In this study, biochemical remission is defined as a fCAL concentration ≤250 µg/g.
f. FMS response: decrease from baseline total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥1 or absolute rectal bleeding subscore ≤1.[12]
g. Remission: a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0.[12]
h. Mucosal healing: a Mayo endoscopic subscore of ≤1.[12]
i. According to treating physician's assessment of bowel wall thickness, normalization and extension; bowel wall vascularity, loss of stratification, loss of colonic haustration, structure formation and hyperechogenic reaction adjacent to the bowel wall.
j. According to treating physician's observations and assessments.

3.1. Variables

Table 4. Study Variables

Variable	Role	Data source(s)	Operational definition
Tofacitinib			
Tofacitinib intake	Exposure	Participant medical records/ CRF	Documentation by treating physician of tofacitinib prescription including doses.
Tofacitinib doses	Exposure, Effect-modifier, Sub-group identifier		
PMS			
Stool frequency	Baseline characteristics & Outcome	Participant medical records/ CRF	Documentation by treating physician of PMS score at baseline and at Week 8 and 16 visits.
Rectal bleeding			
Physician's global assessment			
PROs			
Stool frequency	Outcome	Answers reported by participant and captured in Sidekick Health IBD App	Participants receive notifications to their mobile phone to answer study questionnaires at predefined timepoints according to protocol schedule.
Rectal bleeding			
Urgency of defecation			
Abdominal Pain			
Quality of sleep			
Daily Fatigue			
Weekly fatigue			
Disease-specific quality of life			
fCAL analysis			
fCAL measurements at POC	Outcome	Quantitative result (in µg/g) given after analysis with Quantum Blue® (BÜHLMANN Laboratories AG) device and cassette.	Participants will collect stool samples at home using pre-filled CALEX® Cap Extraction Devices (BÜHLMANN Laboratories AG) and will send their samples to POC for analysis.

Variable	Role	Data source(s)	Operational definition
Patient demographics and medical history			
Year and month of birth	Baseline characteristics	Participant medical records/ CRF	Documentation by treating physician of participant demographics and medical history.
Gender	Baseline characteristics		
BMI	Baseline characteristics		
Smoking status	Baseline characteristics		
Co-morbidities, including EIMs	Effect modifier, Sub-group identifier, Potential confounder		
Concomitant medication	Effect modifier, Sub-group identifier, Potential confounder		
Disease characteristics			
Advanced therapy history	Baseline characteristics, Effect modifier, Sub-group identifier	Participant medical records/ CRF	Documentation by treating physician of all treatments received since UC diagnosis, including dosages, duration and reason for discontinuation.
Safety and Pharmacovigilance			
Incidence of (S)AEs related to drug or to study interventions	Outcome	Study (S)AEs forms and logs, medical records and Pharmacovigilance database	Treating physician will report (S)AEs as per study and usual pharmacovigilance requirements and document events in study (S)AEs forms and logs and medical records.

4. STUDY DESIGN

4.1. Overall Design

This study is an open-label, prospective, low-interventional, multi-center study conducted in Switzerland in a real-world setting uncontrolled by any comparison groups. Approximately 60 adults who are prescribed tofacitinib for moderately to severely active UC will be enrolled in the study. It is expected that a large proportion of enrolled participants will have prior exposure to TNF-antagonists, as tofacitinib is commonly prescribed in this population in Switzerland.

Importantly, no additional endoscopy will be performed and data will only be used from endoscopies and intestinal ultrasound assessments performed as SOC and at physician's discretion.

Although the main focus will be on the first 8 weeks of induction therapy, participants will be additionally followed-up at Week 16 to allow inclusion of data from participants with an insufficient response at 8 weeks. The active study period starts at participant signature of ICD, obtained not later than the first day of tofacitinib treatment initiation and continues for the entire 8-week induction period, and additionally at Week 16. Data collected up to 42 days prior to first day of tofacitinib initiation (ie, baseline visit) can be used for study purposes and analyses. The safety reporting period will extend for an additional 4 weeks (28 days) after the Week 16 visit, or after the discontinuation/withdrawal date for participants who discontinue the study prematurely. Safety reporting is further described in Section 8.3. Participants will continue to receive standard medical care from their treating physician beyond Week 16, independently of end of study period or study outcomes.

This study has 2 minimal risk and burden protocol-required interventions: home stool collection for fCAL concentration measurements and digital collection of PROs through the research version of the Sidekick Health IBD App installed on study participants' personal mobile phone (refer to Section 6 for further details).

4.2. Scientific Rationale for Study Design

This study is designed to enable a characterization of the relationship between changes in PMS, PROs and intestinal inflammation during tofacitinib induction therapy. To fully capture the 16-week induction period and account for delayed responders, PROs will be recorded in all participants at Week 16. Due to the likelihood that some participants will stop therapy or change doses of tofacitinib during the second 8-week period, data during this period will be analyzed in an exploratory fashion. A study-specific research version of the Sidekick Health IBD App is designed to conveniently collect PROs at predefined timepoints according to the study protocol.

To allow valuable insights into the sensitivity and timing of early fCAL responses with respect to disease activity and symptom changes during induction therapy, regular and convenient measurements of fCAL concentrations are designed in this study. To evaluate fCAL responses as predictors of induction therapy outcome, fCAL concentrations will be measured more often during the first week of induction therapy (4 times), followed by measurements on a weekly basis during the following weeks and up to Week 8. An additional measurement is planned at Week 16.

4.2.1. Rationale for Contraception/Pregnancy Testing

To date, no adequate and well-controlled clinical studies have been performed with the use of tofacitinib during pregnancy and there are no data on the transplacental passage of tofacitinib. However, tofacitinib was shown to be teratogenic in rats and rabbits and caused effects on the fertility of female rats, on the parturition and peri- and postnatal development of young rats.

The current approved Swiss label for Xeljanz®[13] (tofacitinib) does not recommend Xeljanz® be administered during pregnancy unless clearly necessary and recommends the use of an effective contraception method for WOCBP while under treatment with Xeljanz® and for at least 4 weeks following treatment termination.

This protocol, however, does not require pregnancy testing prior to inclusion and during the study, nor does it require the use of an adequate method of contraception during the study period. WOCBP who are not using an adequate method of contraception under routine care, or who are not willing to use effective contraception during the study period will not be excluded from the study. Investigators are however advised to monitor WOCBP as per their standard routine clinical practice.

4.2.2. Strengths and Limitations of the Research Methods

Potential limitations exist in collecting regular individual PROs as these are highly variable and subjective. It is believed that participants build a cognitive representation of their disease, including beliefs around the cause, symptoms, consequences and duration, which subsequently guides their behaviors in terms of disease management. Patient disease perceptions may influence their symptoms experiences, with negative beliefs associated with worsening symptoms and burden, even in the absence of active disease. To minimize these potential confounding factors, PROs collected in this study are based on established and validated questionnaires and do not include any free-text questions. Using a digital technology to collect PROs may have several advantages such as convenience, real-time tracking of patient symptoms and quality of collected data. Nevertheless, as this digital App may not be compatible with all mobile phones and operating systems, a risk of bias in the selection of study participants is introduced. Moreover, UC is common in people aged 60 and above, who may be less willing to use innovative technologies on mobile phones, or may simply not own a compatible mobile phone, and would thus be excluded from participating in the study. However, in today's digital era and in a Swiss setting, exclusion rate due to the use of a digital technology is anticipated to be reasonably low.

This real-world study aims to enhance the external validity (ie, the generalizability) of real-world data compared to data from randomized clinical trials, which have restrictive inclusion criteria. The eligibility criteria of this study are designed to reduce bias and to avoid the exclusion of selected populations. Furthermore, participating investigators are gastroenterologists treating IBD patients in both private and public institutions across Switzerland, further increasing generalizability to the Swiss patient population in this study.

4.3. Justification for Dose

Doses of tofacitinib treatment should be based on the Swiss label recommendations, as well as clinical and individual needs, and are determined by the treating physician. The standard tofacitinib induction dosing is 10 mg twice daily for at least 8 weeks, after which the dosage is reduced to the recommended maintenance dose of 5 mg twice daily, although prolongation of the 10 mg twice daily dose up to 16 weeks is permitted if clinically indicated. If off-label doses are used, patient will still be included in the study.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all study procedures, including Week 16 study visit, as well as safety monitoring 28 days following the Week 16 visit.

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the study globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants 18 years of age or older at screening visit;

Type of Participant and Disease Characteristics:

2. Participants with confirmed diagnosis of UC and who are prescribed tofacitinib (Xeljanz®) for moderately to severely active UC as per the Swiss label[13] and as per physician's clinical judgement, independently of this study;

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, study interventions (Section 6), and other study procedures (Section 8);

Informed Consent:

4. Capable of giving personally signed informed consent as described in Appendix 1 10.1.4, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Presence of clinical findings suggestive of Crohn's disease;

Prior/Concomitant Therapy:

2. Any previous exposure to tofacitinib including participation in the tofacitinib clinical program;

3. Co-medication with any other advanced therapies for UC (biologics*, azathioprine, mercaptopurine and methotrexate) or any other JAK inhibitor.

**TNF, integrin or cytokine antagonists.*

Other Exclusions:

4. Any identified contra-indications for use of tofacitinib as per the Swiss label.[13]

5. Not owning a handheld digital device compatible with the Sidekick Health App, not willing to have it installed on this device or not capable of using the App;

6. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

To account for the observational and real-world clinical setting of this study, study protocol does not encourage any changes to the smoking, physical activity and dietary habits of the participants.

For the purposes of this protocol, BMI and smoking status will be assessed at baseline as part of patient demographics data and will be subject to sub-group analysis in an exploratory fashion.

5.3.1. Contraception

Based on preclinical data, tofacitinib has a potential risk of teratogenicity and early fetal loss. Due to this risk, the current approved Swiss tofacitinib label recommends the use of an effective contraception method for WOCBP while under treatment with Xeljanz® and for at least 4 weeks following treatment termination.

This protocol, however, does not require the use of an adequate method of contraception during the study period. WOCBP who are not using an adequate method of contraception under routine care, or who are not willing to use effective contraception during the study period will not be excluded from the study. Investigators are however advised to monitor WOCBP as per their standard routine clinical practice.

5.4. Screen Failures

Screen failures are defined as:

- Participants who are eligible, consent to participate in the clinical study but are not subsequently enrolled in the study (baseline visit is not performed or protocol -required procedures at baseline are missing). Screen failure data are collected and remain as source and are not reported to the clinical study database (ie, CRF).
- Individuals for whom eligibility criteria were checked but who do not meet the criteria for participation in this study. Non eligible individuals may not be rescreened.

Each study site will keep a Screening log to document study Screen Failures and reason for failure. Screen failures will not be enrolled in the study.

6. STUDY INTERVENTIONS

In this study, there are no therapeutic study interventions, however the study does involve protocol-required diagnostic and monitoring procedures (interventions) that are considered to pose only minimal risk or burden to the study participant, specifically:

1. Home stool collection using CALEX® Cap Collection Sets for subsequent fCAL measurements at POC;

2. Collection of PROs using participant's Sidekick Health IBD App research account on their personal mobile phone.

6.1. Study Intervention(s)

6.1.1. Diagnostic or Monitoring Study Interventions

Home stool collection using CALEX® Cap Collection Set for fCAL measurements at POC

Study participants will be introduced, at baseline visit, to the convenient and hygienic stool specimen collection system intended for home use. Each study participant will receive at the beginning of the study a container containing 15 CALEX® Cap Collection Sets. These Sets should be stored at room temperature. Each CALEX® Cap Collection Set contains:

- 1 CALEX® Cap Extraction device pre-filled with extraction buffer (5 mL).
- 2 stool collection sheets.
- 1 study paper card: pre-filled with participant's study ID and an empty field for date and time of sample collection to be completed by the participant.
- 1 illustrated instruction for use leaflet in English, German and French.
- 1 transparent resealable bag.
- 1 pre-paid and pre-addressed UN3373 packaging.

Although 12 stool collections are planned according to Table 2, 3 extra CALEX® Cap Collection Sets will be provided to participants at the beginning of the study. This is to account for any collection procedure failures or other unexpected reasons requiring the use of additional sets.

Between study visits, and according to Table 2 schedule, the participant will use a CALEX® Cap extraction device to collect at home a standardized amount of stool sample in a buffered solution, as illustrated in the instruction for use leaflet. The participant must indicate the date and time of sample collection on the provided paper card, place the CALEX® Cap extraction device in the provided transparent resealable bag and then place the latter in the pre-paid and pre-addressed UN3373 packaging provided. Lastly, the participant will post the packaging by normal postal mail on the same day or on the next day at the latest, for fCAL concentration measurements at POC.

As fCAL concentrations decrease with increasing time between bowel movements, participants will be advised to collect stool samples for fCAL testing from the first bowel movement of the day. Because of the day-to-day variability in fCAL levels, participants will be advised to collect their stool samples at a similar time throughout the study.

Collection of PROs using Sidekick Health IBD App on participant's mobile phone

Upon study inclusion (ie, baseline visit), participants will have to download the Sidekick Health App to their personal mobile phone. If a participant is already using the Sidekick Health App before enrollment to the study, he/she will be able to continue using the functionalities of the native App. However, for study purposes, each participant will be given a unique study login to initiate their research account for the App and will be introduced to the different functionalities of the App. No personal data (eg, name, surname, personal email or address) will be captured in the research-version of the App, the participant will be identified solely by his/her unique study ID and study email. Site staff will ensure the App is working correctly and that the participant is able to use it. Participants who are not willing to adhere to PRO questionnaires procedure and schedule, or not willing to download or use the study Sidekick Health IBD App, will not be able to participate in the study, as defined by study exclusion criteria.

Between study visits, participants will be prompted to complete the PRO questionnaires within the Sidekick Health IBD App on their mobile phone via pop-up notifications at predefined timepoints (as described in Table 2) and at the same time every day. Participants can choose the language (German/French) in which they wish to receive the questionnaires and use the App. It is estimated that full completion of all questionnaires will require no more than 10 minutes per day. Participants will be prompted to complete the questionnaires via pop-up notifications from the App. In the event the participant's mobile phone is switched off, out of battery, or the participant forgets to fill-in the questionnaires, a reminder will be sent the following day and if necessary a study nurse will attempt to contact the participant by phone, after which the data will be treated as missing. Participants will be informed about the importance to respond to questionnaires whenever required. Data captured in the App will be transferred to the study database on a regular basis.

6.2. Preparation/Handling/Storage/Accountability

The following instructions apply to the CALEX® Cap Collection Sets, referred to as study interventions in this section:

1. Study site investigator or designee must confirm that appropriate conditions have been maintained during transit from *central supply* for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. All study interventions must be stored in an appropriate and secured environment with controlled access to authorized site staff only.

3. Study interventions should be kept in the original packaging as received from *central supply*. Study interventions will be labelled by site staff with participant study ID before they are dispensed.

4. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply study intervention to enrolled participants. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

5. Site staff must ensure appropriate records are maintained for study intervention accountability. Accountability records will account for received study interventions from *central supply* and study interventions dispensed to enrolled participants.

6. At the end of the study period for each participant, all unused study interventions must be returned to the investigator by the participant and recorded in the accountability records. Returned study intervention must not be re-dispensed to other participants. At site closure, all unused study interventions must be returned to *central supply.*

7. *Applies to POC only:* all received study interventions containing biospecimens must be stored appropriately and in a secured and controlled environment. POC staff must ensure appropriate records are maintained for study intervention accountability. Accountability records will account for received study interventions from study participants, analyzed study interventions and destroyed study interventions. All destructions must be adequately documented. Destruction is authorized to take place at POC and POC staff must ensure that the materials and biological samples are destroyed in compliance with the study Biospecimen Management Plan, applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Central Supply: Preparation and Dispensing

All study interventions needed for the entire study period will be ordered with BÜHLMANN Laboratories AG, Switzerland and sent to *central supply.* Herein, *central supply* refers to GALSER SA in Switzerland. Reconditioning of the original BÜHLMANN Laboratories AG packaging will be performed by qualified staff member of the *central supply*; containers containing CALEX® Cap Collection Sets with other necessary materials. *Central supply* will ensure that:

- All study interventions are stored in an appropriate and secured environment with controlled access to authorized staff only.
- Appropriate records are maintained for study intervention accountability. Accountability records will account for received study interventions from BÜHLMANN Laboratories AG and study interventions dispensed to study sites.
- Study sites are supplied with adequate quantities of study interventions at the appropriate time.

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

7.1. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. The study investigator and/or study sponsor may decide to discontinue a participant from the study. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up (Section 7.2);
- Death;
- Study terminated by sponsor;
- Withdrawal of consent (Section 7.1.1);
- Any other justified reason.

In this study, drug under study refers to tofacitinib. Participants who stop tofacitinib treatment for any reason during the study, will not be discontinued/withdrawn.

Participant will remain in the study and all protocol-required assessments until Week 16 must be completed. Participants who discontinue tofacitinib treatment prior to end of study will be included in the ITT analysis. Treatments received following tofacitinib discontinuation will be recorded as part of study data.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. Refer to the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study.

Participants who decide to withdraw from the study, should be questioned regarding their reason for withdrawal, but do not have to justify their decision.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for disclosure of future information (Section 7.1.1), no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.1.1. Withdrawal of Consent

Participants should notify the investigator in writing of the decision to withdraw consent for future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal was from study procedures and/or study follow-up, and this information should be entered on the appropriate CRF page.

7.2. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a protocol-required study visit and/or cannot be contacted for follow-up:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or equivalent method). These contact attempts should be documented in the participant's study record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Participants who discontinue the study prior to the Week 8 visit, for any of the above reasons, will be replaced by enrolling new participants.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol-required study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed. SOC assessments for which data will be collected if available and their timing, are also summarized in the SoA.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue from the study.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Every effort should be made to ensure that protocol-required tests and procedures (study interventions) are completed as described. However, it is anticipated that there may be circumstances outside the control of the investigator that may make it infeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol -required procedure cannot be performed, the investigator will document the reason for the missed procedure and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. Such incidents will be documented in a Study Protocol Deviation Form or in a Note to File. The study team must be informed of these incidents in a timely manner. Due to COVID-19 pandemic, adapted measures are permitted if they are deemed necessary to ensure the rights, safety and well -being of study participants. Such measures should be clearly documented and communicated to study sponsor in a timely manner.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened, or record reasons for screening failure, as applicable. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific (protocol-required) procedures.

Procedures conducted as part of the participant's routine clinical management (eg, laboratory tests, endoscopy, IUS) and recorded in the medical record prior to the participant signing of the ICD may be utilized for screening or baseline purposes provided the procedures were performed within the time frame defined in the SoA.

For samples being collected and shipped, detailed collection, processing, storage, shipment and destruction instructions, as well as contact information are detailed in the Biospecimen Management Plan and will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Protocol-required Assessments

8.1.1.1. PMS Assessment

The 12-point Mayo score is an instrument designed to measure UC disease activity based on a combination of endoscopic findings and the patient's clinical characteristics.[40] The non-invasive PMS excludes the endoscopic component of the full Mayo scoring system and ranges from 0 to 9 points. The PMS consists of the following 3 subscores, each graded from 0 to 3, with higher scores indicating more severe disease:

- Stool frequency (0-3);
- Rectal bleeding (0-3);
- Physician global assessment (0-3).

Stool frequency subscore assessment:

- 0 = Normal number of stools;
- 1 = 1–2 stools more than normal;
- 2 = 3–4 stools more than normal;
- 3 = 5 or more stools than normal.

Rectal bleeding subscore assessment:

- 0 = No blood seen;
- 1 = Blood streaks seen in stool less than half the time;
- 2 = Blood seen in stool most of the time;
- 3 = Blood alone passes.

Physician global assessment subscore assessment:

- 0= Normal;
- 1= Mild Colitis;
- 2= Moderate Colitis;
- 3= Severe Colitis.

Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency. The daily rectal bleeding score represents the most severe bleeding of the day. The physician global assessment subscore acknowledges the 2 other subscores (stool frequency and rectal bleeding), patient's recollection of abdominal discomfort, general sense of wellbeing, and other observations, such as physical findings and patient's performance status.

It is recommended that the same physician performs all such assessments for a particular study participant throughout the study.

PMS will be assessed at the baseline, Week 8 and Week 16 visits. Failure to assess PMS at these study visits will constitute a protocol deviation.

Endpoints based on the Partial Mayo scores are defined as follows:

- Clinical remission: total PMS of ≤2 with no subscore exceeding 1 point;[12]

- Clinical response: meeting one of the following criteria: (1) reduction in PMS of ≥2 points from baseline or (2) achieving clinical remission as described above.[12]

The FMS will be calculated if endoscopy is performed as SOC. The Mayo Endoscopic subscore assessed as SOC and PMS assessed as protocol-required assessment will be used to calculate FMS. Endoscopy is not a protocol-required procedure, nor a mandatory assessment for inclusion in the study.

8.1.1.2. PROs Assessment

The Sidekick Health IBD App installed on participants' personal mobile phones will be used to collect PROs during the study. PROs are collected between study visits. Via their personal mobile phone, participants will be provided with brief PRO questionnaires that encompass important elements of the subjective experience of UC. PROs will be collected daily until Week 2 and thereafter twice weekly until Week 8. Participants will receive training from qualified staff and important information related to the App and the study questionnaires in writing. Responses to questionnaires are time-stamped and will be reviewed for completeness by automated predefined processes and rules. Participants will receive notifications to input PROs at scheduled timepoints, according to study protocol.

It is important to note that PROs are collected and evaluated in a different manner than the observed AEs. Given these differences, no attempt will be made to resolve any apparent discrepancies between experienced AEs and PRO data collected from participants. AE incidence rates will not be assessed from PRO data but from information recorded on the study dedicated AEs forms and related CRF pages.

Table 5 details the various study PROs and the related instrument for collection:

Table 5. PROs and Related Instrument for Collection

PRO	Instrument	Description
Stool frequency	Participant will answer the question "How many times did you need to visit the toilet to have a bowel movement today?" using the stool frequency subscore of Mayo scoring system.[40,41]	Scores range from 0 to 3 and higher scores indicate more severe disease activity: • 0 = Normal number of stools; • 1 = 1–2 stools more than normal; • 2 = 3–4 stools more than normal; • 3 = 5 or more stools than normal. Each participant serves as his or her own control to establish the degree of abnormality of stool frequency.
Rectal bleeding	Participant will answer the question "How would you describe the blood in your stool today?" using the rectal bleeding subscore of Mayo scoring system.[40,41]	Scores range from 0 to 3 and higher scores indicate more severe disease activity: • 0 = No blood seen; • 1 = Streaks of blood with stool less than half the time; • 2 = Obvious blood with stool most of the time; • 3 = Blood alone passes. The daily bleeding score represents the most severe bleeding of the day. Each participant serves as his or her own control to establish the degree of rectal bleeding.
Urgency of defecation	NRS to respond to "How severe was your urgency (sudden or immediate need) to have a bowel movement in the past 24 hours?", according to Dubinsky et al.[42]	11-point horizontal NRS anchored at 0 ("No urgency") and 10 ("Worst possible urgency"). Participant can input a score from 0 to 10.
Abdominal pain	NRS to answer the question "How much abdominal pain have you felt today?" according to Spiegel et al.[43]	10-point horizontal NRS anchored at 1 ("None") and 10 ("Very severe"). Participant can input a score from 1 to 10.
Quality of sleep	NRS to answer the question "How did you sleep last night?", based on Rubin et al.'s Sleep VAS.[27]	11-point horizontal NRS anchored at 0 ("Very bad") and 10 ("Great"). Participant can input a score from 0 to 10.
Daily fatigue	NRS to respond to "Please rate your fatigue (weariness, tiredness) by selecting the number that describes your worst level of fatigue during the past 24 hours" according to Gladman et al.[44]	11-point horizontal NRS anchored at 0 ("no fatigue") and 10 ("as bad as you can imagine"). Participant can input a score from 0 to 10.

PRO	Instrument	Description
Weekly fatigue	FACIT-F for weekly measurements of fatigue.[45]	FACIT-F: 13-point questionnaire; responses to each question are recorded on a 5-point Likert scale. Scores range from 0 to 52, with higher scores representing greater fatigue. Participant responses are based on symptoms felt during the last 7 days.
Disease-specific quality of life	IBDQ[46]	32-item questionnaire grouped into 4 dimensions: bowel function, emotional status, systemic symptoms and social function. The 4 domains are scored as follows: • Bowel symptoms: 10 to 70; • Systemic symptoms: 5 to 35; • Emotional function: 12 to 84; • Social function: 5 to 35. The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. Questionnaire is designed to collect data from the previous 2 weeks.

Endpoints based on collected PROs are defined as follows:

- IBDQ remission: total IBDQ score of ≥170;
- IBDQ response: increase in IBDQ score from baseline of ≥16 points;
- MCID in the FACIT-F score: minimum individual change in the FACIT-F score from baseline of 3.[45]

8.1.1.3. fCAL Concentrations Assessment

All fCAL measurements will be performed in batches at 1 central study site (central POC) by an appropriately trained study nurse. CALEX® Cap devices containing biospecimens will be stored at 2-8°C until they are analyzed, after which they will be destroyed according to local practices and as described in the Biospecimen Management Plan. Both investigators and participants will be blinded to the results of fCAL measurements throughout the study. Investigators may perform independent fCAL assessments, in addition to those mandated by the protocol, if such assessments are deemed appropriate and necessary for the participant's disease management. Results from these independent fCAL measurements will not be recorded in the CRF nor reimbursed.

fCAL measurements will be performed using the BÜHLMANN Laboratories AG Quantum Blue® device and the Quantum Blue fCAL extended test cassette (LF-CALE25), which is a lateral flow test developed using the same monoclonal antibodies as the gold-standard ELISA. Once the CALEX® Cap Extraction devices arrive at POC, they are ready to be analyzed, and no further manipulation is required. The range of the test is 30 to 1000 µg/g.

To obtain fCAL measurements, 60 ul of the solution in the CALEX® Cap device is loaded onto a test cassette. During the mandatory 12 min incubation time, fCAL present in the sample binds to gold-coated monoclonal antibodies present on the test membrane. The solution proceeds along the membrane over 12 minutes to a test line, where antibodies specific to the anti-fCAL complexes are bound, darkening the test line. A second line with anti-fCAL antibodies serves as a reference control that the Quantum Blue® reader compares based on image analysis. A lot-specific standard curve on the device is used to calculate the result in micrograms of fCAL per gram of stool sample (µg/g) and the quantitative result is displayed on the device screen. Measurements obtained on Quantum Blue® device will be entered manually to the corresponding eCRF page by central POC study nurse or an authorized study member, independent of patient care.

Optimal fCAL cut-off values for the detection of active disease vary from 50 µg/g to 250 µg/g [2,38,47] depending on the test used, location of the disease and intra-individual patient variability. In this study, biochemical remission is defined as a fCAL concentration ≤250 µg/g.[11]

In addition to the protocol-required procedures described above, the following data will be collected and is required for compliance with study protocol:

- Patient demographics including month and year of birth, gender and BMI upon inclusion in the study (at baseline).
- Baseline smoking status defined as: current smoker, former smoker or never smoked.
- UC disease characteristics; advanced treatment history including reason for treatment change or discontinuation. Advanced treatment history is collected at baseline, per SoA.
- Tofacitinib exposure dose throughout the study duration.
- All concomitant medications, especially corticosteroids and 5-ASA.
- All co-morbidities, including EIMs.
- All serious and non-serious adverse events (refer to Section 8.3).

8.1.1.4. Other Assessments

Additional data will be collected to address further exploratory objectives:

- **Discontinuation incidence**: study-specific discontinuation form will be used to collect reason for study or drug discontinuation, clinical and other undertaken procedures at discontinuation, as well as outcome, where applicable.

- **Unscheduled visits**: in the event where the participant requires an on-site visit in addition to the scheduled visits listed in the SoA table, these visits will be documented in study-specific unscheduled visits forms. The unscheduled visits form will be used to collect reason of additional visits, clinical and other procedures undertaken during such visits, as well as outcome, where applicable.

8.1.2. SOC Assessments

This study protocol intends to collect the assessments described below in an observational manner only. If any of the following assessment is missing, it will not constitute a protocol deviation.

Patient medical records will be referred to for SOC assessment reports or results. The participant is aware that his/her medical records will be consulted as part of this study. The treating physician or study site staff will grant access to these records, securely kept, and managed locally on site as per standard procedures.

The following data will be collected, if available, and reported into the corresponding pages of the CRF:

- UC disease characteristics: date of diagnosis and extent. Extent will be assessed if colonoscopy is performed and defined as either ulcerative proctitis, proctosigmoiditis, left-sided colitis or pancolitis;

- CRP level: concentration in mg/L and date of test.

Mayo Endoscopic subscore. Mayo Endoscopic subscore and PMS assessed as protocol-required assessment will be used to calculate FMS. FMS will only be calculated if endoscopy is performed as part of SOC and according to physician's assessment. Mayo Endoscopic subscore calculation:

0= Normal or inactive disease.

1= Mild disease (erythema, decrease of vascular pattern, slight friability).

2= Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3=Severe disease (spontaneous bleeding, ulceration)

- IUS:[48]
    - Measurement (in mm) of colonic wall thickness at all colon parts (ascending, transverse, descending and sigmoid) and of rectal wall thickness;

- Evaluation of the extension of wall-thickening according to physician's observations;
- Evaluation of normalization of wall-thickening according to physician's observations;

- Evaluation (yes, no) for: loss of stratification, loss of colonic haustration, structure formation and hyperechogenic reaction adjacent to the bowel wall;
- Evaluation of bowel wall vascularity according to Limberg score:[53]

  0= no bowel wall thickening, no vascularization

  1= bowel wall thickening without vascularization

  2 (hypo-flow)= bowel wall thickening with short stretches of vascularity as spots

  3 (hyper-flow)= bowel wall thickening with longer stretches of vascularity

  4 (hyper-flow)= bowel wall thickening with longer stretches of vascularity reaching the mesentery

Endoscopy or IUS images will not be retrieved as part of study records. Only evaluations and physician's reported observations will be recorded as study records.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements or other safety assessments may be obtained at any time during the study to assess any perceived safety issues.

Safety data are collected for the purpose of meeting routine pharmacovigilance reporting requirements. Safety data will not be analyzed, but simply reported on a case-by-case basis.

8.2.1. Protocol-Required Clinical Safety Laboratory Assessments

Protocol-required clinical safety laboratory assessments will not be performed in this study.

8.2.2. Pregnancy Testing

To date, no adequate and well-controlled clinical studies have been performed with the use of tofacitinib during pregnancy and there are no data on the transplacental passage of tofacitinib. However, tofacitinib was shown to be teratogenic in rats and rabbits and caused effects on the fertility of female rats, on the parturition and peri- and postnatal development of young rats.

The local approved label for Xeljanz® does not recommend Xeljanz® be administered during pregnancy unless clearly necessary. However, this study does not require pregnancy testing prior to inclusion.[13]

8.3. Adverse Events and Serious Adverse Events

In a LIS2 "product under study" refers to the drug, therapeutic medical device or the vaccine product (or any active comparator or placebo) that is under study in the LIS2. Herein, "product under study" refers to tofacitinib (Xeljanz®).

The definitions of an AE, SAE and RRI can be found in Appendix 2 (10.2). The investigator is required to assess whether any AE may be related to participation in the study. All AEs (ie, serious and non-serious, including those attributed to a protocol-required procedure identified as RRI) are collected in the clinical study database. Should a participant, in the investigator's opinion, suffer a medically important RRI caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or they may arise from clinical findings of the investigator or other HCPs (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (Section 7.1).

During the active safety collection period (Section 8.3.1), each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information ("Active Collection Period")

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any protocol-required procedure), through and including a minimum of 28 calendar days, after the Week 16 visit, or after the discontinuation/withdrawal date.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues the product under study because of an AE or SAE, prior to all scheduled doses having been administered, then the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively solicit AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the product under study, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1, are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 2 (10.2). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All SAEs and non-serious AEs occurring during the active collection period (Section 8.3.1) must be recorded in the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2 (10.2).

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until the event has resolved, stabilizes or is otherwise explained, or the participant has been lost to follow-up (as defined in Section 7.2).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2 (10.2).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the product under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Environmental Exposure

The requirements for reporting pregnancy or breastfeeding and environmental/occupational exposure apply throughout the entire active collection period and are outlined below; when such reports are required per protocol, the report must be transmitted to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy EDP

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing the product under study.
- A male participant who is receiving or has discontinued the product under study exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to the product under study due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the product under study by ingestion.
    - A male family member or healthcare provider who has been exposed to the product under study by ingestion then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected for the clinically-relevant time period.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedural test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator considers that the infant death may be related to exposure to the product under study.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing the product under study.
- A female is found to be breastfeeding while being exposed or having been exposed to the product under study (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the product under study by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a product specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Environmental Exposure

An environmental exposure, including an occupational exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with, or exposure to, the product under study. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members and others who may be exposed.

The investigator must report any instance of environmental exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form. This form must be used to report the exposure even if no SAE is associated with the exposure.

Since the information about the exposure does not pertain to a participant enrolled in the study, the information is not recorded on the CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is the failure of expected pharmacologic action or therapeutic benefit of the product under study.

Lack of efficacy is collected in the CRF but is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the product under study by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Table 6. Reporting of Medication Errors

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the product under study;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

- The administration of expired drug;
- The administration of an incorrect drug;
- The administration of an incorrect dosage;
- The administration of the product under study that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the product in question is acceptable for use.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

Sponsor does not recommend specific treatment for an overdose; a specific antidote does not exist. A symptomatic treatment is recommended according to the Swiss approved label.

Refer to Section 8.3.10 Medication Errors for reporting requirements for an overdose.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Not applicable.

8.8. Biomarkers

The following samples for biomarker research are protocol-required and will be collected from all participants during the study as specified in the SoA:

- Participant stool sample collection for fCAL concentration measurements.

Stool samples for fCAL concentration measurements will be collected to evaluate response to tofacitinib induction therapy and to verify the validity of fCAL concentrations as a convenient surrogate biomarker to assess early response to tofacitinib therapy (secondary endpoints). Stool samples will be collected with BÜHLMANN's stool extraction device, the CALEX® Cap Collection Set. Samples will be analyzed centrally at the POC using BÜHLMANN's 3rd generation Quantum Blue® Reader, a monoclonal antibodies lateral flow test. Samples will be destroyed immediately after analysis according to local practices and the Biospecimen Management Plan. No further sample storage or use is planned.

8.9. Immunogenicity Assessments

Immunogenicity assessments will not be performed in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study hypotheses that will be subject to statistical testing are that:

- Tofacitinib induction therapy is associated with a rapid improvement in the PMS, intestinal inflammation (ie, reduced fCAL concentrations), QoL and symptoms (PROs).
- Changes in different types of treatment outcomes (ie, PMS, PROs and fCAL concentrations) are correlated.
- Improvements in PROs and fCAL concentrations can predict treatment outcomes (clinical outcome measures) at end of induction therapy.

9.2. Sample Size Determination

Based on PMS data from the OCTAVE Induction and RW studies, feedback from Swiss gastroenterologists on drop-out rates during the first 8 weeks of tofacitinib therapy and assuming that most participants will have prior exposure to TNF-antagonists, we estimated that a sample size of 60 participants should be sufficient to detect a significant reduction from baseline in PMS at Week 8.

Thus, a total of approximately 60 study participants will be enrolled into the study. A participant is considered enrolled if protocol-required procedures at baseline visit are performed. An enrolled participant who discontinues the study before Week 8 study (ie, Week 8 visit is not performed), will be replaced by enrolling a new participant. The main aim of the study is to describe the frequency of participants achieving a clinical response after 8 weeks of treatment with a given precision. There will be no formal hypothesis testing; frequencies will be estimated with 95% Wilson confidence intervals.

We expect that 60% of participants will achieve a clinical response at Week 8 (ie, effect size based on data from a RW study with a comparable study population).[7] A sample of 60 participants will result in a 2-sided 95% Wilson confidence interval[55] around a frequency of 60% from 47.4 to 71.4%.

In the OCTAVE Induction studies, the mean change in PMS from baseline at Week 8 was approximately -3.1 and the standard deviation in PMS at baseline was approximately 1.3.[12] Thus, if we assume a standard deviation in PMS of 1.3 at baseline and at Week 8, the worst-case scenario would be that the standard deviation for mean change in PMS between baseline and Week 8 amounts to 2.6. Thus, a sample size of 60 participants and a standard deviation in change in PMS from baseline of 2.6, would yield a 95% confidence interval with a width of ±0.66 points (ie, power >95% to detect a -3.1 change from baseline), able to detect a difference as low as -1.2, with 90% power.

9.3. Data Management

The Data Management system used in this study is a dedicated EDC system, SecuTrial. The EDC system is activated for the study only once a formal test procedure has been passed successfully. All data entered in the EDC system are stored on a Linux server in a dedicated Oracle database at Inselspital Bern, Switzerland. The Clinical Trial Unit of Inselspital is responsible for study data management activities (implementation and maintenance of the study database).

Study-related data of the participant will be collected in a coded manner. The names of the participants will not be disclosed. A code (unique, consecutive numbered per site) will be attributed to each participant registered in the eCRF. A codebook will be created describing the datasets and all variables to be collected and the associated coding.

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission of each user for system and database use.

All data entered into the eCRFs are transferred to the database using TLS encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. A multi-level back-up system is implemented.

At final analysis, data files will be extracted from the database into statistical packages to be analyzed. After database lock, the status of the database is recorded in special archive tables.

9.4. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer collectively to both pCRF and eCRF.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and paper form and will be password protected and secured in a locked room to prevent access by unauthorized third parties.

The investigator has the ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the pCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. eCRFs have an audit trail functionality to track all modifications.

In this study, some source documents are the hospital or the physician's chart. Data collected on the CRFs must match those charts. Study source documents are further described in Appendix 1 (10.1.8).

9.5. Data Analysis

9.5.1. Datasets to be Analyzed, Analysis Population

Study protocol adherence will be assessed based on adherence to fCAL measurements and PROs questionnaires completion. Adherence to tofacitinib will not be assessed.

a. ITT analysis will include participants who were included in the study (ie, performed baseline visit and received a study identification number). This analysis will therefore include all study participants, regardless of their adherence to study protocol procedures.

b. PP analysis will include all study participants who, at the end of the study, met the following criteria:

   - fCAL measurements: At least 6 stool samples out of 12 are collected and provided (ie, 50% of fCAL measurements), including a baseline stool sample (ie, baseline fCAL concentration is available)

   - For each PRO, the participant has completed at least 50% of the scheduled questionnaires, as well as the baseline questionnaire. A PRO questionnaire is deemed completed if all items of the questionnaire have been answered.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.5.2. Primary Analysis

Proportions of participants achieving clinical, IBDQ and biochemical response* and remission† at Week 8 and Week 16 will be calculated and reported with the associated 95% Wilson confidence interval.

The course of continuous secondary outcomes (PROs and fCAL) over time will be depicted by box plots showing medians, quartiles, and outlying values.

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* Clinical response: (1) Reduction in PMS from baseline of >2 points or (2) achieving clinical remission.[12]

IBDQ response: IBDQ score ≥16 points higher than IBDQ baseline score.

† Clinical remission: PMS of ≤2 with no subscore >1.[12]

IBDQ remission: IBDQ score ≥170.[12]

Biochemical remission: fCAL concentration ≤250 mg/g.[11]

Correlation between PMS, PROs, IBDQ score and fCAL concentrations will be assessed by the Spearman correlation coefficient.

The course of fCAL over time will be shown separately for participants with and without clinical response, as well as for participants with and without remission at Week 8 and Week 16.

These analyses will also be conducted on the subset of participants that complete 8 weeks of tofacitinib therapy.

9.5.3. Secondary Analysis

The following baseline characteristics were identified to potentially modify the treatment effect:

1. Prior exposure to TNFi, vedolizumab and ustekinumab;
2. Concomitant medication with corticosteroids and/or aminosalicylic acids;
3. Predominant tofacitinib dose.

These characteristics will be used for stratified analyses.

The effect of participants' baseline characteristics on change in PMS, PROs and fCAL values will be investigated using generalized mixed models for repeated measurements.

Moreover, proportions of:

- Participants achieving FMS response[‡] at W8;
- Participants achieving remission[§] at W8;
- Participants achieving FMS response at W16;
- Participants achieving remission at W16;
- Participants achieving mucosal healing[**] at W8;
- Participants achieving mucosal healing at W16;
- Participants achieving response according to IUS assessment[††] at W8;
- Participants achieving remission according to IUS assessment at W8;
- Participants achieving response according to IUS assessment at W16;

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‡ FMS response: Decrease from baseline total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥1 or absolute rectal bleeding subscore of ≤1.[12]

§ Remission: a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0.[12]

** Mucosal healing: a Mayo endoscopic subscore of ≤1.[12]

†† According to treating physician's assessment of bowel wall thickness, normalization and extension; bowel wall vascularity, loss of stratification, loss of colonic haustration, structure formation and hyperechogenic reaction adjacent to the bowel wall.

- Participants achieving remission according to IUS assessment at W16;
- Participants with improvement in EIM (individual or categorical)[‡‡] at W8;
- Participants with improvement in EIM (individual or categorical) at W16.

will be reported with the associated 95% Wilson confidence interval.[55]

9.6. Interim Analyses

Not applicable.

9.7. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a Data Monitoring Committee.

‡‡ According to treating physician's observations and assessments.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the Sponsor/CRO and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Sponsor/CRO will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Further country specific requirements are described in Appendix 4 10.4.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the product under study, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Responsible Parties

Sponsor Team

- PPD **, MD, PhD,** PPD, UK.
- PPD **, PhD,** PPD, Switzerland.
- PPD **, PhD,** PPD, Switzerland.
- PPD **, PhD,** PPD

Pfizer Clinician and medical monitor

- PPD, MD PPD

Principal Investigator

- **Christoph Matter, MD** Senior Gastroenterologist and internist, Intesto, Gastroenterologische Praxis Crohn-Colitis Zentrum, Bremgartenstrasse 119, 3012 Bern.

Study Statistician

- PPD **, PhD,** Pfizer Inc., PPD.

Data Management and Statistical analysis

- **Clinical Trial Unit Bern**, Mittelstrasse 43, 3012 Bern.

Monitoring institution

- **GALSER SA,** Swiss CRO, Rue des Beaux-Arts 8, 2000 Neuchâtel.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10.1.4. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The participant's medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) if the ICD is revised during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.5. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and paper form and will be password protected and secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law. Authorized study staff will be listed and documented in a Study Delegation Log, under the investigator's responsibility.

To protect the rights and freedoms of participants with regards to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. Only authorized staff will have access to the code list. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed and/or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring) methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on- site monitoring), are provided in the central monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing SDV to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, the participant’s current medical record must be available.

Definition of what constitutes source data can be found in the Central Clinical Monitoring Plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.9. Study and Site Start and Closure

The study site start date is the date on which the clinical study will be open for recruitment of participants at the study site, following the SIV.

The first act of recruitment is the date of the first study participant’s first visit and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

The investigator agrees that the results of the study will be published exclusively under the coordination of the sponsor and will include the results of all participating centers. For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator agrees that the first publication is to be a joint Publication covering all Study sites, and that any subsequent publications will reference that primary Publication.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

In a LIS2 "product under study" refers to the drug, therapeutic medical device or the vaccine product (or any active comparator or placebo) that is under study in the LIS2. Herein, "product under study" refers to tofacitinib (Xeljanz®).

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of the product under study, whether or not considered related to the product under study.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the product under study.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
    - Is associated with accompanying symptoms.
    - Requires additional diagnostic testing or medical/surgical intervention.
    - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
    - Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the product under study even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the product under study or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death.**

b. **Is life-threatening.**

   The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Research Related Injury

Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;
- Is life threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.2.3. Definition of Medication Error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the healthcare professional, patient, or consumer. Such events may be related to:

- Professional practice,
- Procedures,
- Systems, including:
    - Prescribing;

- Order communication;
- Product labeling, packaging, and nomenclature;
- Dispensing;
- Distribution;
- Administration;
- Education;
- Monitoring;
- Use.

Medication errors also include near-misses involving or not involving a patient directly or confusion regarding invented names (eg, trade name, brand name).

10.2.4. Definition of Overdose

An overdose is an administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information.

10.2.5. Recording/Reporting and Follow-up of AEs and/or SAEs during the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety throughout the active collection period(s). These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the product under study or any Pfizer product used under routine care during pregnancy or breastfeeding, or an environmental/occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Table 7. Reporting of Safety Events

Safety Event	Record on CRF	Report on the CT SAE Report Form to Pfizer Safety within 24 hours of awareness
SAEs	All SAEs occurring during the active collection period(s).	All SAEs occurring during the active collection period(s). Any SAEs (including death) that occur after the active collection period(s) and the investigator suspects may be related to the product under study. Important note: for an SAE where it cannot be excluded that the event is attributable to the sampling of biological material or the collection of health-related personal data, the event must only be reported on the Swissethics Serious Event Report form to the CRO immediately upon awareness. Refer to Appendix 4 (10.4) for more information.
Non-serious AEs	All non-serious AEs occurring during the active collection period(s)	None.
Scenarios involving EDP and EDB.	Any AE or SAE associated with EDP or EDB. **Note:** Instances of EDP or EDB not associated with an AE/SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE).* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study by a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE/SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or Occupational exposure:** AEs/SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report form.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between the product under study and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to administration of the product under study, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the product under study caused the event, then the event will be handled as "related to product under study" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible.

This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.6. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

The country specific requirements for the recording and reporting of SAE occurring during the active collection period(s) are outlined in Appendix 4 (10.4).

10.3. Appendix 3: Liver Safety: Suggested Actions and Follow up Assessments - Potential Cases of Drug Induced Liver Injury

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or overthecounter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.4. Appendix 4: Country Specific Requirements

10.4.1. Switzerland

Local regulations/Declaration of Helsinki

This study will be conducted in accordance with the protocol, the Declaration of Helsinki,[§§] the principles of Good Clinical Practice, the HRA[***] and the HRO,[†††] as well as other local relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO).
Type of Research Project:	Research project involving human subjects
Risk Categorization:	Risk category A acc. to ordinance HRO Art.7
Project Leader/Sponsor:	Pfizer AG, Schärenmoosstrasse 99, 8052 Zürich, Switzerland

GCP Training

Before enrolling any participants, the investigator and any sub-investigators will complete a Good Clinical Practice training course recognized by Swissethics ("GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study related duties. For studies of applicable duration, the investigator and sub-investigators will complete GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

Study Intervention

No participants or third-party payers will be charged for study intervention. Study intervention does not refer to product under study (Xeljanz®), which will be charged to participant's health insurance as per routine practice.

[§§] Declaration of Helsinki.
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects).

[***] Human Research Act (HRA).
http://www.admin.ch/opc/en/classified-compilation/20121176/201401010000/810.305.pdf.

[†††] Ordinance on Human Research with the Exception of Clinical trials (HRO) https://www.admin.ch/opc/en/classified-compilation/20121177/index.html.

Liability Coverage

This study is exempt from liability coverage requirements according to Art. 12 HRO.

Obligations of safety communication to Ethics Committee

- **Notification of safety and protective measures (HRO Art. 20).**

The investigator notifies the CRO and the Sponsor, within 24 hours, in case immediate safety and protective measures have to be taken during the conduct of the study. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

- **Serious events (HRO Art. 21)**

If a serious event‡‡‡ occurs, the investigator should notify the CRO and the Sponsor within 24 hours of awareness. The CRO will notify the Ethics Committee via BASEC within 7 days. In addition, the investigator shall assess the connection between the event and the collection of health-related personal data or the sampling of the biological material. At the same time, proposals concerning the corrective and preventive measures to be taken should be submitted. The Ethics Committee shall reach a decision on the continuation of the study within 30 days after receipt of the report.

Serious events will be recorded using the Swissethics Serious Event Report form for HRO research projects and submitted to the Ethics Committee.

Compensation to study participants

Participants will not be compensated for their participation in the study. However, if the study participant is asked to come to the study site for any procedures related only to the study and which are not part of regular medical care, he/she will be reimbursed for expenses that result from the travel to the site (for example, transportation fees or parking), CCI [redacted].

‡‡‡ A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.
A SE may also be a RRI as defined in APPENDIX 2 10.2.2 and should be reported to the Pfizer clinician immediately.

Substantial and non-substantial amendments

Substantial amendments to the study set-up, the protocol and relevant study documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants. Substantial amendments are changes that affect the safety, health, rights and obligations of study participants, changes in the protocol that affect study objective(s), changes of study site(s) or of study leader and sponsor.

End of study

Upon project completion or discontinuation, the Ethics Committee is notified within 90 calendar days. All biological materials and health-related data are anonymized upon termination of data analysis.

Funding, publication policy and declaration of interest

The study is initiated and funded by Pfizer AG.

A description of the study will be available on www.kofam.ch (n°SNCTP xxx) as required by Swiss law.

Participating investigators declare no conflict of interest.

10.5. Appendix 5: Protocol Specific Appendices

Sidekick Health IBD App

At the end of the study (ie, after completing Week 16), study participants will be asked to complete the user version of the Mobile Application Rating Scale (uMARS)[54] to rate the Sidekick Health IBD App used in this study. A shortened version of the uMARS including only sections A-E will be used. Thus, the questionnaire will include 23 questions separated into 5 sections including App engagement, functionality, aesthetics, information and participants' subjective App quality assessment. Completion of this questionnaire will not be mandatory as per study protocol, ie, study participants can choose to not respond to this questionnaire. Missing data will therefore not be considered protocol deviation.

All study related data collected on the App will be stored on the App provider's cloud-based platform in Belgium during the entire study duration and will be imported to the study database in Switzerland on a regular basis. Study related will be transferred to the Sponsor in a coded form and data are entirely owned by the Sponsor of the study. At the end of the study, the data will be deleted from the Sidekick Health database and this data destruction will be documented in a relevant certificate of destruction. Data collected on the App and transferred to the study database, will be archived together with other study data according to applicable regulations.

Participants who choose to use the functionalities from the native (non-research) version of the Sidekick Health IBD App (eg, IBD-specific modules, activity logging, food diary), which are freely accessible to study participants via their App research account, and thereby choose to provide personal information, such as information about their diet, physical activity, vital signs, etc., will be informed that all these non-research data will be collected and stored by Sidekick Health. Importantly, these non-research data collected via native App functionalities will not be linked to the research data or to individual study participants. Sidekick Health might, at the end of the study, use the data collected via native App functionalities to assess the usability of these App features by the study participants during the study duration. All data collected and assessed will be anonymized and expressed in an aggregated form.

The Full Terms and Conditions and Privacy Policy of Sidekick Health are available under the following links: https://legal.sidekickhealth.com/2/en/terms.html and https://legal.sidekickhealth.com/2/en/privacy.html, respectively.

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations used in the protocol:

Table 8. Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
App	mobile application
AST	aspartate aminotransferase
BASEC	Business Administration System for Ethical Committees
BMI	body mass index
CD	Crohn's Disease
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CT	clinical trial
DILI	drug-induced liver injury
eCRF	electronic case report form
EDB	exposure during breastfeeding

Abbreviation	Definition
EDC	electronic data capture
EDP	exposure during pregnancy
EIM	extra-intestinal manifestation
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
fCAL	fecal calprotectin
FMS	Full Mayo score
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HRA	Human Research Act
HRO	Human Research Ordinance
HRQL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IBS	irritable bowel syndrome
ICD	informed consent document

Abbreviation	Definition
ICH	International Council for Harmonisation
ID	identification
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IUS	intestinal ultrasound
JAKi	Janus Kinase inhibitor
LFT	liver function test
LIS2	low-Interventional Study 2
MCID	minimal clinically important difference
MSR	Medical & Scientific Relations manager
NA	not applicable
NRS	numerical rating scale
pCRF	paper case report form
PMS	Partial Mayo score
POC	point of care
PP	per-protocol
PRO	patient reported outcome
PT	prothrombin time
QoL	quality of life
RRI	research related injury
RW	real world

Abbreviation	Definition
RWD	real world data
RWE	real world evidence
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDV	source data verification
SIV	site initiation visit
SNCTP	Swiss National Clinical Trials Portal
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBili	total bilirubin
TLS	Transport Layer Security
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analogue scale
W# *(where # is a number)*	Week # of study
WOCBP	woman of childbearing potential

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