UNIVERSITÄT BERN
Faculty of Medicine
CTU Bern

Statistical Analysis Plan (SAP)

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

Administrative Information

Project number:	1594
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Revision history

Revision	Justification	Timing

Approved by

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1. Glossary of abbreviations

CRF	Case Report Form
EDC	Electronic Data Capturing system
FAS	Full Analysis Set
fCAL	Fecal calprotectin
IBDQ	Inflammatory Bowel Disease Quality of Life
ICD	Informed Consent Document
IUS	Intestinal Ultrasound
OTAS	On-Tofacitinib Analysis Set
PMS	Partial Mayo Score
PP	Per-Protocol analysis set
PRO	Patient-Reported Outcome
(S)AE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
UC	Ulcerative Colitis
W	Week

Contents

2. Introduction

2.1 Background and rationale

A number of studies have been published demonstrating tofacitinib's safety and efficacy profile in ulcerative colitis (UC) [1-8]. While it is known that tofacitinib therapy is associated with a rapid onset of symptom relief in terms of the Partial Mayo score (PMS) components (stool frequency and rectal bleeding), the response of other important patient-reported outcomes (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, the response of intestinal inflammation to tofacitinib induction therapy is currently not fully understood [11]. Regular measurements of fecal calprotectin (fCAL) levels, a widely used biomarker in UC, will provide a measure of the response of intestinal inflammation to tofacitinib treatment. Early measurements will assess the validity of fCAL as an early biochemical predictor of treatment response.

2.2 Objectives

This study aims to generate granular real-world data on tofacitinib therapy in UC and enable a characterization of the relationship between changes in PMS, PROs and intestinal inflammation during tofacitinib induction therapy.

3. Study methods

3.1 Trial design

This study is a single-arm, open-label, prospective, low-interventional, multi-center study conducted in Switzerland in a real-world setting without any comparison groups. Approximately 60 participants were planned to be enrolled. However, following the termination decision as per Pfizer CT26-GSOP, recruitment was prematurely stopped after the enrollment of 18 patients. Please see Section 9 for details on the resulting changes to endpoints and analysis specified in the protocol.

3.2 Randomization

Not applicable.

3.3 Sample size

The initial sample size calculation was shown in the final version of the protocol (22 March 2022). According to that calculation, a total of approximately 60 participants were planned to be enrolled into the study. However, following an internal decision by Pfizer, recruitment was prematurely stopped after the enrollment of 18 patients.

We expect that 60% of participants will achieve a clinical response at Week 8. As noted in the protocol, a sample of 60 participants would have result in a 2-sided 95% Wilson confidence interval around a frequency of 60% from 47.4 to 71.4%. A sample of 18 participants will result in a 2-sided 95% Wilson confidence interval around a frequency of 60% from 37.6 to 78.9%.

3.4 Framework

This is a descriptive single-arm study, there will be no formal hypothesis testing.

3.5 Statistical interim analyses and stopping guidance

Not applicable.

3.6 Timing of final analysis

Final analysis will be performed after database lock.

3.7 Timing of outcome assessments

All outcomes will be analyzed collectively after study completion. After completion of data entry, data validation and cleaning will be performed. Data analysis will start after database lock.

3.8 Blinding

The study is unblinded.

4. Data management

4.1 Data export

The Data Management system used in this study is a dedicated electronic data capturing (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.

Clinical study data will be provided by CTU Bern (Clinical Trial Unit of the University of Bern) in a database format (secuTrial®) and will be imported into R by the study statistician for data preparation, validation, and analysis.

4.2 Data validation

First line data validation is performed by the online Case Report Form (eCRF) system in real-time as defined in the data dictionary. Second line data validation and cleaning will be performed according to the Standard Operating Procedure (SOP) for data validation [13] after the completion of overall data collection, before database export for the final analysis.

4.3 Data preparation

Table 4-a: Data preparation

Variable definition	Variable type	Derivation
Baseline date: date of first medication intake	Date (dd.mm.yyyy)	`pro_medi_start_date`
Prior exposure to TNFi, vedolizumab and ustekinumab;	Binary (yes, no)	Used variables: th_ustekinumab th_vedolizumab th_tnfi Visit: Baseline. Derivation - General: 'yes' if at least one of the above variables is different from 'Never prescribed'; 'No' otherwise. - if missing data (i.e., at least one of the 3 variables mentioned above is missing): 'yes' if at least one of the above variables is different from "Never prescribed"; 'NA' otherwise.
Concomitant medication with corticosteroids or aminosalicylic acids	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end `pro_medi_start_date` Derivation If `cm_drug.factor` contains "Topical corticosteroids" OR "Oral corticosteroids" OR "Topical aminosalicylates" OR "Oral aminosalicylates"

Variable definition	Variable type	Derivation
		AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of Ustekinumab	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Ustekinumab" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of Vedolizumab	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Vedolizumab" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of TNF inhibitors	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "TNF inhibitors" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of Tacrolimus	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Tacrolimus" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of Cyclosporin	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Cyclosporin" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of Methotrexate	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date

Variable definition	Variable type	Derivation
		Derivation If cm_drug.factor contains "Methotrexate" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of Thiopurines	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Thiopurines" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of aminosalicy-lates	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Oral / topical aminosalicylates" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of steroids	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date Derivation If cm_drug.factor contains "Topical corticosteroids" OR "Oral corticosteroids" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end])
Concomitant use of low dose ster-oids	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date cm_dose Derivation If cm_drug.factor contains "Topical corticosteroids" OR "Oral corticosteroids" AND if one of the mentioned above drugs is taken at the pro_medi_start_date (i.e. pro_medi_start_date %in% [cm_start, cm_end]) with the dose (i.e. cm_dose) %in% c('Systemic: < 15mg/day prednisone equivalent' , 'Locally-acting: < 3mg/day budesonide')
Concomitant use of high dose steroids	Binary (yes, no)	Used variables: cm_drug.factor cm_start cm_end pro_medi_start_date cm_dose Derivation If cm_drug.factor contains "Topical corticosteroids" OR

Variable definition	Variable type	Derivation
		"Oral corticosteroids" AND if one of the mentioned above drugs is taken at the `pro_medi_start_date` (i.e. `pro_medi_start_date` %in% [`cm_start, cm_end`]) with the dose (i.e. cm_dose) %in% c('Systemic: ≥ 15mg/day prednisone equivalent' , 'Locally-acting: ≥ 3mg/day budesonide')

Baseline predominant tofacitinib dose	Binary (<15mg tofacitinib/day, ≥15 mg tofacitinib/day)	Variable:
		`te_bl_dose.factor`
		`te_bl_dose_oth_value`
		`te_bl_dose_oth_unit`
		Visit:
		Baseline.
		Derivation
		'yes' if `te_bl_dose.factor` == '10 mg twice daily' OR `te_bl_dose.factor` == 'Other' & (`te_bl_dose_oth_value` & `te_bl_dose_oth_unit` <15 mg/day) ;
		otherwise 'no'.

Average daily dose of Tofacitinib during the trial	Binary (<15mg tofacitinib/day, ≥15 mg tofacitinib/day)	Variable:
		`te_bl_dose.factor`
		`te_bl_dose_oth_value`
		`te_bl_dose_oth_unit`
		`te_dose`
		`te_other_value`
		`te_other_unit`
		`te_start`
		`te_end`
		`te_disc_date`
		Derivation:
		Calculation of the mean daily dose of tofacitinib and categorization as < 15mg/day or ≥ 15mg/day

IBDQ score	Continuous (score varying between from 32 to 224)	Variables: `pro_ibdq_x` (with X varying from 1 to 32) Derivation: at each reported time point. For each variable, 7 answers are possible. Answers are ranked from the 'worst' to 'best' quality of life, and replaced by a score varying from 1(worst) to 7(best). Scores obtained for each of the 32 variables are then summed up. If any of the `pro_ibdq_x` (with X varying from 1 to 32) variables is missing the score is coded as missing.
Weekly fatigue score (FACIT-F score)	Continuous (score varying between from 0 to 52)	Variables `pro_facit_an1, pro_facit_an2, pro_facit_an3, pro_facit_an4, pro_facit_an5, pro_facit_an7, pro_facit_an8, pro_facit_an12, pro_facit_an14, pro_facit_an15, pro_facit_an16, pro_facit_hi12, pro_facit_hi7` Derivation: at each reported time point. For each variable, 5 answers are possible. Answers are converted to score (see below), scores obtained for each of the 13 listed variables are then summed up. If any of the variables use to derive the score is missing the score is coded as missing.

Variable definition	Variable type	Derivation
		Scoring system: Not at all =0; A little bit =1; Somewhat =2; Quite a bit =3; Very much =4
PMS score	Continuous	Variables: `pms_stool_freq, pms_rect_bleed, pms_glob_ass` Derivation: At each reported time point. For each variable, 4 answers are possible. Answers are converted to score from 0 (normal) to 3 (more severe condition), scores obtained for each of the 3 listed variables are then summed up. If any of the variables use to derive the score is missing the score is coded as missing.
PMS stool frequency subscore	Continuous	Variable: `pms_stool_freq` Derivation: At each reported time point. 4 answers are possible. Answers are converted to score from 0 (normal) to 3 (more severe condition).
PMS rectal bleeding subscore	Continuous	Variable: `pms_rect_bleed` Derivation: At each reported time point. 4 answers are possible. Answers are converted to score from 0 (normal) to 3 (more severe condition).
PMS physician's global assessment subscore	Continuous	Variable: `pms_glob_ass` Derivation: At each reported time point. 4 answers are possible. Answers are converted to score from 0 (normal) to 3 (more severe condition).
Full Mayo score	Continuous	Variables: `PMS score (see above), ra_mayo_subscore` Derivation: At each reported time point. For each variable, 4 answers are possible for the `ra_mayo_subscore` variable. Answers are converted to score from 0 (normal) to 3 (severe disease), scores obtained for the PMS score and the `ra_mayo_subscore` variable are then summed up. If any of the variables use to derive the score is missing the score is coded as missing.
Participant's age	Continuous	Used variables: `ic_date, ymob` Derivation: Date of signature of the inform consent in mm.yyyy – the date of birth in mm.yy. Result is given in year and rounded to one decimal point
EIM improvement status at week_x (x can be equal to 8 or 16)	Continuous	Variables: `eim_cat, eim_subcat_muco, eim_subcat_muscu, eim_subcat_ocular, eim_subcat_hepa, eim_activity` Derivation: For each EIM (defined by the variables `eim_cat, eim_subcat_muco, eim_subcat_muscu, eim_subcat_ocular, eim_subcat_hepa`) ▪'No worsening' if

Variable definition	Variable type	Derivation
		eim_activity at baseline =' Active at assessment' AND eim_activity at week_x =' Active at assessment' OR eim_activity at baseline =' Past, but not active' AND eim_activity at week_x =' Past, but not active' OR EIM at baseline AND EIM not mentionned at week_x ▪'Worsened' if eim_activity at baseline =' Past, but not active' AND eim_activity at week_x =' Active at assessment' ▪'Improved' if eim_activity at baseline =' Active at assessment' AND eim_activity at week_x =' Past, but not active' ▪'New occurence' if No EIM at baseline AND eim_activity at week_x =' Active at assessment'
Number of comorbidities	Continuous	Used variables: co_morb_yn co_morb Derivation: at bl, W8 and 16. If co_morb_yn== 'yes' count the number of different entries for co_morb If co_morb_yn== 'no' 0
Number of EIMs	Continuous	Used variables: eim_yn Derivation: at bl, W8 and 16. If eim_yn== 'yes' count the number of different entries for EIM If eim_yn== 'no' 0
uMARS score	Continuous	Sum all uMARS answers (variables names not available at the time of writing the SAP). If any of the variables use to derive the score is missing, the score is coded as missing.

5. Statistical principles

5.1 Confidence intervals and *P* values

All confidence intervals will be two-sided and relate to the 95% level and the two-sided significance level will be set at α = 0.05.

5.2 Analysis populations

5.2.1 Full analysis set (FAS)

The full analysis set (FAS), will include all participants who were included in the study (i.e., 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.

5.2.2 Per-protocol analysis set (PP)

Not applicable.

5.2.3 On-tofacitinib analysis set (OTAS)

The on-tofacitinib analysis set consists of all participants in the FAS set who did not stop or interrupt the tofacitinib therapy before the 8 weeks visit.

Table 5-a: Derivation of protocol deviations

Protocol deviation	eCRF sheet	Variable	Variable type	Derivation
Completion of the therapy until the W8 visit	Binary (yes, no)	Used variables: Time to tofacitinib discontinuation (see above) Date of the 8 weeks visit Derivation 'yes' if Time to tofacitinib discontinuation (see above) < Date of the 8 weeks visit	Completion of the therapy until the W8 visit	Binary (yes, no)

5.2.4 Safety population

Not applicable

6. Study Population

6.1 Screening data

All screening evaluations will be entered in the database. In case of screening failure, reason(s) for failure will be recorded.

6.2 Eligibility

6.2.1 Inclusion Criteria

Age and Sex:

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

Type of Participant and Disease Characteristics:

- Participants with confirmed diagnosis of UC and who are prescribed tofacitinib (Xeljanz®) for moderately to severely active UC as per the Swiss label [14] and as per physician's clinical judgement, independently of this study;
- Participants who are willing and able to comply with all scheduled visits, treatment plan, study interventions (Section 6 of the protocol), and other study procedures (Section 8 of the protocol).

Informed Consent:

- Capable of giving personally signed informed consent (as described in Section 10.1.4 of the protocol), which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICD) and in the protocol.

6.2.2 Exclusion Criteria

Medical Conditions:

- Presence of clinical findings suggestive of Crohn's disease;

Prior/Concomitant Therapy:

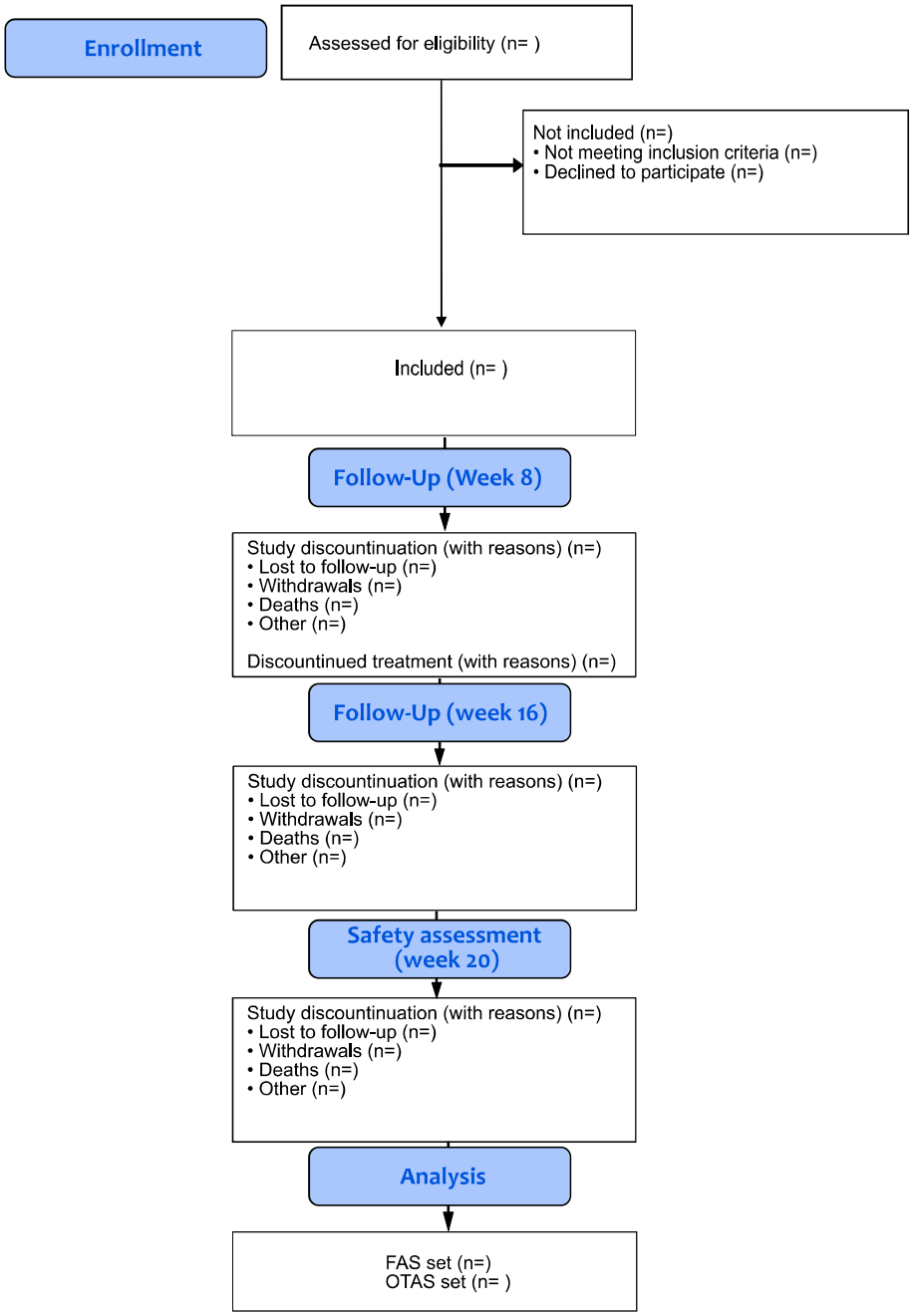
- Any previous exposure to tofacitinib including participation in the tofacitinib clinical program;
- Co-medication with any other advanced therapies for UC (biologics*, azathioprine, mercaptopurine and methotrexate) or any other JAK inhibitor.
  **TNF, integrin or cytokine antagonists.*

Other Exclusions:

- Any identified contra-indications for use of tofacitinib as per the Swiss label [14];
- 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;
- 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.

6.3 Recruitment

A CONSORT patient flow diagram will be drawn following the CONSORT 2010 standards [15].



6.4 Baseline patient characteristics

The patient characteristics at baseline will be presented in a table, as number and percentage or mean and standard deviation for categorical and normally distributed continuous variables, respectively. For data severely deviating from a normal distribution, we will present median and quartiles.

Table 6-a: Baseline table

Description	Variable	Type
Patient demographics		
Age (year of birth)	`ic_date` and `ymob` (see data preparation `4.3`)	Continuous: years
Gender	`sex`	Binary: Male, Female
BMI	`dg_bmi`	Continuous
Smoking status	`dg_smoking`	Categorical: Never smoked, Former smoker, Current smoker
Concomitant medication at baseline		
Concomitant medication with corticosteroids or aminosalicylic acids	see data preparation 4.3	Binary: Yes, No
▪ Concomitant use of steroids	see data preparation 4.3	
▫ Concomitant use of low dose steroids	see data preparation 4.3	
▫ Concomitant use of high dose steroids	see data preparation 4.3	Binary: Yes, No
Concomitant use of Ustekinumab	see data preparation 4.3	Binary: Yes, No
Concomitant use of Vedolizumab	see data preparation 4.3	Binary: Yes, No
Concomitant use of TNF inhibitors	see data preparation 4.3	Binary: Yes, No
Concomitant use of Tacrolimus	see data preparation 4.3	Binary: Yes, No
Concomitant use of Cyclosporin	see data preparation 4.3	Binary: Yes, No
Concomitant use of Methotrexate	see data preparation 4.3	Binary: Yes, No
Concomitant use of Thiopurines	see data preparation 4.3	Binary: Yes, No
Concomitant use of aminosalicylates	see data preparation 4.3	Binary: Yes, No
UC medication		

Description	Variable	Type
Baseline predominant tofacitinib dose	see data preparation 4.3	Binary: < 15mg; or ≥ 15mg tofacitinib/day
Main UC disease characteristics		
PMS	see data preparation 4.3	Continuous
PMS stool frequency subscore	see data preparation 4.3	Continuous
PMS rectal bleeding subscore	see data preparation 4.3	Continuous
PMS physician's global assessment subscore	see data preparation 4.3	Continuous
UC treatment history		
Prior exposure to TNFi,vedolizumab and ustekinumab	`th_ustekinumab`, `th_vedolizumab`, and `th_tnfi` at baseline (see data preparation 4.3)	Binary: Yes, No
▪ Prior exposure to TNFi	`th_tnfi_nr` at baseline ('no' if `th_tnfi_nr` = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No
▫ Number of TNFi	`th_tnfi_nr`	Binary: 1, >1
▫ Prior exposure to oral & topical aminosalicylates	`th_amino`	Categorical: Never prescribed, Lack of/ insufficient response, Loss of response, Intolerance/side effects, Treatment ongoing, Unknown
▫ Prior exposure to Locally acting & systemic corticosteroids (e.g. budesonide, prednisone)	`th_cortico`	Categorical: Never prescribed, Lack of/ insufficient response, Loss of response, Intolerance/side effects, Treatment ongoing, Unknown
▫ Prior exposure to Thiopurines (e.g. AZA, 6-MP)	`th_thiopur`	Categorical: Never prescribed, Lack of/ insufficient response, Loss of response, Intolerance/side effects, Treatment ongoing, Unknown
▫ Prior exposure to Other immunosuppressants (e.g. cyclosporine, tacrolimus)	`th_immunosup`	Categorical: Never prescribed, Lack of/ insufficient response, Loss of response, Intolerance/side effects, Treatment ongoing, Unknown
▫ Prior exposure to TNF inhibitors (TNFi)	`th_tnfi`	Categorical: Never prescribed, Lack of/ insufficient response, Loss of response, Intolerance/side effects, Treatment ongoing, Unknown
▪ Prior exposure to vedolizumab	`th_vedolizumab` at baseline ('no' if `th_vedolizumab` = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No

Description	Variable	Type
▪ Prior exposure to ustekinumab	th_ustekinumab at baseline ('no' if th_usteki-numab = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No
Prior exposure to oral & topical ami-nosalicylates	th_amino at baseline ('no' if th_amino = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No
Prior exposure to lo-cally acting & sys-temic corticosteroids (e.g. budesonide, prednisone)	th_cortico at baseline ('no' if th_cortico = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No
Prior exposure to Thiopurines (e.g. AZA, 6-MP)	th_thiopur at baseline ('no' if th_thiopur = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No
Prior exposure to IMP	th_imp at baseline ('no' if th_imp_yesno="no" OR th_imp = 'Never prescribed', 'yes' other-wise)	Binary: Yes, No
Prior exposure to other treatment	th_imp at baseline ('no' if th_other_yesno ="no" OR th_other = 'Never prescribed', 'yes' otherwise)	Binary: Yes, No
· Other immunosup-pressants (e.g. cy-closporine, tacroli-mus)	th_immunosup	
SOC Intestinal Ultra Sound (IUS)		
For Ascending, de-scending, Sigmoid and transverse co-lon at W8 & 16 Extension of wall-thickening	ra_[*]_col_ext [*] = – 'asc' for Ascending colon – 'desc' for descending colon – 'sig' for Sigmoid colon – 'trans' for transverse colon	Binary: Yes, no
For Ascending, de-scending, Sigmoid and transverse co-lon at W8 & 16 Normalization of wall-thickening	ra_[*]_col_norm [*] = – 'asc' for Ascending colon – 'desc' for descending colon – 'sig' for Sigmoid colon – 'trans' for transverse colon	Binary: Yes, no
Loss of stratification at W8 & 16	ra_loss_strat	Binary: Yes, no
Loss of colonic haustration at W8 & 16	ra_loss_col_haus	Binary: Yes, no

Description	Variable	Type
Structure formation at W8 & 16	ra_struct_form	Binary: Yes, no
Hyperechogenic reaction adjacent to the bowel wall	ra_hyper_react	Binary: Yes, no
Co-morbidities, including extra-intestinal manifestations		
Co-morbidities		
Number of comorbidities	see data preparation 4.3	Continuous
Extraintestinal Manifestations (EIM)		
Identified EIM	eim_yn	Binary: yes, no
Number of EIMs	see data preparation 4.3	Continuous
▪ Mucocutaneous	eim_cat ('yes' if eim_cat = 'Mucocutaneous', 'no' otherwise)	Binary: yes, no
▫ Psoriasis	Variables: eim_subcat_muco & eim_activity Derivation: 'no eim' if eim_subcat_muco≠'Psoriasis', 'Active at assessment' if eim_subcat_muco = 'Psoriasis' AND eim_activity='Active at assessment', 'Past but not active ' if eim_subcat_muco = 'Psoriasis' AND eim_activity='Past but not active')	Categorical: no EIM, Active at assessment, Past but not active
▫ Erythema nodosum	Variables: eim_subcat_muco & eim_activity Derivation: same as for Psoriasis, replacing 'Psoriasis' by 'Erythema nodosum'	
▫ Pyoderma gangrenosum	Variables: eim_subcat_muco & eim_activity Derivation: same as for Psoriasis, replacing 'Psoriasis' by 'Pyoderma gangrenosum'	
▫ Aphthous stomatitis	Variables: eim_subcat_muco & eim_activity Derivation: same as for Psoriasis, replacing 'Psoriasis' by 'Aphthous stomatitis'	
▫ Other	Variables: eim_subcat_muco & eim_activity Derivation: same as for Psoriasis, replacing 'Psoriasis' by 'Other'	

Description	Variable	Type
▪Musculoskeletal	eim_cat ('yes' if eim_cat='Musculoskeletal', 'no' otherwise)	
▫ Inflammatory arthritis	Variables: eim_subcat_muscu & eim_activity Derivation: 'no eim' if eim_subcat_muscu ≠'Inflammatory arthritis ', 'Active at assessment' if eim_subcat_muscu = 'Inflammatory arthritis' AND eim_activity = 'Active at assessment', 'Past but not active ' if eim_subcat_muscu = 'Inflammatory arthritis' AND eim_activity = 'Past but not active')	Binary: Active at assessment, Past, but not active
▫ Other	Variables: eim_subcat_muscu & eim_activity Derivation: same as for Inflammatory arthritis, replacing 'Inflammatory arthritis' by 'Other'	
▪Ocular	eim_cat ('yes' if eim_cat='Ocular', 'no' otherwise)	
▫ Uveitis	Variables: eim_subcat_ocular & eim_activity Derivation: 'no eim' if eim_subcat_ocular ≠ 'Uveitis', 'Active at assessment' if eim_subcat_ocular = 'Uveitis' AND eim_activity = 'Active at assessment', 'Past but not active ' if eim_subcat_ocular = 'Uveitis' AND eim_activity = 'Past but not active')	Binary: Active at assessment, Past, but not active
▫ (Epi)scleritis	Variables: eim_subcat_ocular & eim_activity Derivation: same as for Uveitis, replacing 'Uveitis' by '(Epi)scleritis'	
▫ Other	Variables: eim_subcat_ocular & eim_activity Derivation: same as for Uveitis, replacing 'Uveitis' by 'Other'	
▪Hepatobiliary	eim_cat ('yes' if eim_cat = 'Hepatobiliary', 'no' otherwise)	

Description	Variable	Type
▫ Primary sclerosing cholangitis	Variables: `eim_subcat_hepa` & `eim_activity` Derivation: 'no eim' if `eim_subcat_hepa` ≠' Primary sclerosing cholangitis', 'Active at assessment' if `eim_subcat_hepa` = ' Primary sclerosing cholangitis' AND `eim_activity` ='Active at assessment', 'Past but not active ' if `eim_subcat_hepa` = 'Primary sclerosing cholangiti' AND `eim_activity` = 'Past but not active')	Binary: Active at assessment, Past, but not active
▫ Cholangiocarcinoma	Variables: `eim_subcat_hepa` & `eim_activity` Derivation: same as for Primary sclerosing cholangitis, replacing ' Primary sclerosing cholangitis' by 'Cholangiocarcinoma'	
▫ Primary biliary cirrhosis	Variables: `eim_subcat_hepa` & `eim_activity` Derivation: same as for Primary sclerosing cholangitis, replacing ' Primary sclerosing cholangitis' by 'Primary biliary cirrhosis'	
▫ Autoimmune hepatitis	Variables: `eim_subcat_hepa` & `eim_activity` Derivation: same as for Primary sclerosing cholangitis, replacing ' Primary sclerosing cholangitis' by 'Autoimmune hepatitis'	
▫ Other	Variables: `eim_subcat_hepa` & `eim_activity` Derivation: same as for Primary sclerosing cholangitis, replacing ' Primary sclerosing cholangitis' by 'Other'	
Other UC disease characteristics		
Duration of disease (days before baseline from date of UC diagnosis date	`ra_uc_diag_date - ic_date`	Continuous (days)
UC extent (location)	`ra_uc_ext` at baseline	Categorical: Ulcerative proctitis, Proctosigmoiditis, Pancolitis, Left-sided colitis
CRP level	`ra_crp_conc` at baseline	Continuous (mg/L)
Full Mayo score	see data preparation 4.3	Continuous

Description	Variable	Type
Mayo Endoscopic subscore	`ra_mayo_subscore` at baseline	Categorical: Normal or inactive disease, Mild disease (erythema, decrease of vascular pattern, slight friability), Moderate disease (marked erythema, absent vascular pattern, friability, erosions), Severe disease (spontaneous bleeding, ulceration)
Intestinal Ultrasound at baseline	`ra_ultrasound_done`	Binary: Yes, No
fCAL at baseline		
fCAL at baseline	`fcal_value` at baseline	Continuous
PRO at baseline		
Stool frequency	`pro_stool_freq`	Categorical: Normal number of stools", 1-2 stools more than normal, 3-4 stools more than normal, 5 or more stools than normal
Rectal bleeding	`pro_rect_bleed`	Categorical: No blood seen, Blood streaks seen in stool less than half the time, Blood seen in stool most of the time, Blood alone passes
Urgency of defecation	`pro_nrs_urgency`	Continuous
Abdominal pain	`pro_nrs_abd_pain`	Continuous
Quality of sleep	`pro_nrs_qual_sleep`	Continuous
Daily fatigue	`pro_nrs_fatigue`	Continuous
Weekly fatigue	Weekly fatigue score (see data preparation 4.3)	Continuous
Quality of life (IBDQ)	`pro_ibdq_x` (with x varying between 1 and 32) at baseline see data preparation 4.3	Continuous

6.5 Procedural characteristics (if applicable)

Not applicable.

6.6 Adherence and protocol deviations

Adherence to study protocol and to tofacitinib will not be assessed.

Main analysis will be conducted on the full analysis set (FAS). Secondary analysis will include all study participants who did not stop or interrupt the tofacitinib therapy before the week 8 visit (i.e OTAS set, see section 5.2.3).

6.7 Withdrawal/follow-up

Number and percentage of withdrawal and lost to follow-up will be presented in the flow chart (see section 6.3).

7. Analysis

7.1 Outcome definitions

Table 7-a: Derivation of study outcomes

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
PRIMARY OUTCOME						
Clinical response at W8	(1) reduction in PMS from baseline of ≥2 points or (2) achieving clinical remission	PMS	PMS score (see section 4.3) pms_stool_freq pms_rect_bleed pms_glob_ass	continuous	Yes: If (PMS at W8- PMS at baseline≥2) OR PMS at W8 ≤2 AND pms_stool_freq<2 AND pms_rect_bleed<2 AND pms_glob_ass<2 at W8.	Binary: Yes, no
SECONDARY OUTCOMES						
Clinical response at W16	(1) reduction in PMS from baseline of ≥2 points or (2) achieving clinical remission		PMS score (see section 4.3) pms_stool_freq pms_rect_bleed pms_glob_ass	continuous	Yes: If (PMS at W16- PMS at baseline≥2) OR PMS at W16 ≤2 AND pms_stool_freq<2 AND pms_rect_bleed<2 AND pms_glob_ass<2 at W16.	Binary: Yes, no
Clinical remission W8/W16	Clinical remission: PMS of ≤ 2 with no subscore >1		PMS score (see section 4.3) pms_stool_freq pms_rect_bleed pms_glob_ass	continuous	Yes: PMS at W8 (or 16) ≤2 AND pms_stool_freq<2 AND pms_rect_bleed<2 AND pms_glob_ass<2 at W8 (or 16).	Binary: Yes, no

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
IBDQ remission at W8/W16	IBDQ remission: *IBDQ score ≥ 170*		IBDQ score calculated as described in section 4.3 at W8 and 16	continuous	Yes: IBDQ at W8 (or 16) ≥170	Binary: Yes, no
IBDQ response at W8/W16	IBDQ response: IBDQ score ≥16 points higher than IBDQ baseline score		IBDQ score calculated as described in section 4.3 at baseline, W8 and 16	continuous	Yes: IBDQ at W8 (or 16) – IBDQ at BL≥16	Binary: Yes, no
Biochemical remission at W8/W16	Biochemical remission: fCAL concentration ≤*250 µg/g*		`fcal_value`	continuous	Yes: fcal_value≤*250 µg/g*	Binary: Yes, no
PROs						
Stool frequency		Stool freq, rect. bleed, NRS	`pro_stool_freq`	Score (0-3), continuous		Continuous
Rectal bleeding			`pro_rect_bleed`	Score (0-3), continuous		Continuous
Urgency of defecation			`pro_nrs_urgency`	Continuous		Continuous
Abdominal pain			`pro_nrs_abd_pain`	Continuous		Continuous
Quality of sleep			`pro_nrs_qual_sleep`	Continuous		Continuous
Daily fatigue			`pro_nrs_fatigue`	Continuous		Continuous
Weekly fatigue		FACIT-F	`"pro_facit_an1", "pro_facit_an12", "pro_facit_an14","pro_facit_an15",`	Continuous	See section 4.3	Continuous

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
			"pro_facit_an16", "pro_facit_an2", "pro_facit_an3", "pro_facit_an4", "pro_facit_an5", "pro_facit_an7", "pro_facit_an8", "pro_facit_hi12", "pro_facit_hi7".			
IBDQ		PRO IBDQ	pro_ibdq_1 to 32	Continuous	See section 4.3	Continuous
PMS		PMS	PMS score (see section 4.3)	Continuous		Continuous
Clinical response						
fCAL		fCAL	fcal_value	Continuous		Continuous
EXPLORATORY OUTCOMES						
FMS response at W8/W16.	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	PMS & SOC Assessment	ra_full_mayo (calculated as described in section 4.3) pms_rect_bleed	Continuous	[(ra_full_mayo at BL - ra_full_mayo at W8 (or 16)) ⩾3] AND [(ra_full_mayo at BL - ra_full_mayo at W8 (or 16))/ ra_full_mayo at BL ⩾0.3] AND [pms_rect_bleed at BL - pms_rect_bleed at W8 (or W16) ⩾1 OR pms_rect_bleed at W8 (or W16) ⩽1]	Binary: Yes, no

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type

remission at W8/W16	Remission: a total Mayo score of ≤2, with no subscore >1 and a rectal bleeding subscore of 0	PMS & SOC Assessment	`ra_full_mayo` (calculated as described in section 4.3)
			
			`pms_stool_freq`
			`pms_glob_ass`
				continuous	ra_full_mayo at W8/16 ≤2 AND
					[pms_stool_freq ≤ 1 AND pms_glob_ass ≤ 1 at W8/16 AND pms_rect_bleed at W8/16 = 0]
						Binary: Yes, no

mucosal healing at W8/W16.	Mucosal healing: a Mayo endoscopic subscore of ≤1	SOC Assessment	`ra_mayo_subscore`	continuous	ra_mayo_subscore at W8/16 ≤1	Binary: Yes, no
response according to IUS assessment at W8/W16.	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.	SOC Assessment	`ra_global_eval`	categorical	Yes: `ra_global_eval %in% c('response', 'remission')`	Binary: Yes, no
remission according to IUS assessment at W8/W16.	According to treating physician's assessment of bowel wall thickness, nor-	SOC Assessment	`ra_global_eval`	categorical	Yes: `ra_global_eval ='remission'`	Binary: Yes, no

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
	malization and extension; bowel wall vascularity, loss of stratification, loss of colonic haustration, structure formation and hyperechogenic reaction adjacent to the bowel wall.					

individual improvement in EIM reported at BL at W8/W16
15 outcome/variables
	EIM improvement for EIM reported at BL	Extra Intestinal Manifestations (EIM)	`eim_cat`
			`eim_subcat`
			`eim_activity` ('Past, but not active' vs. active at assessment)
				-Categorical
				-Categorical
				- Binary
					See section 4.3 for EIM improvement status at week_x (x can be equal to 8 or 16)
					Yes: EIM improvement status == Improved
						Binary: Yes, no

Categorical improvement 5 variables/outcomes	EIM improvement is reported for at least one of the subcategories of the studied category.	Extra Intestinal Manifestations (EIM)	`eim_cat` `eim_activity` ('Past, but not active' vs. active at assessment)	-Categorical - Binary	Yes: eim_cat==the studied category AND eim_activity=='Past, but not active'	Binary: Yes, no
ADDITIONAL EXPLORATORY OUTCOMES						
Average daily dose of Tofacitinib during the trial		Baseline Tofacitinib Change in Tofacitinib Exposure			See section 4.3	Binary: <15mg tofa-citinib/day,

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
		Tofacitinib discontinuation				≥15 mg tofacitinib/day
Active UC at W8 and 16 based on IUS assessments	active UC: at least one of the measurement of colonic wall thickness >4 mm. missing data are ignored	SOC Assessment, Intestinal Ultrasound	ra_trans_col_meas ra_sig_col_meas ra_desc_col_meas ra_asc_col_meas		ra_trans_col_meas > 4 OR ra_sig_col_meas > 4 OR ra_desc_col_meas> 4 OR ra_asc_col_meas > 4	Binary: active UC, inactive UC
For Ascending, descending, Sigmoid and transverse colon at W8 & 16 Extension of wall-thickening		SOC Assessment, Intestinal Ultrasound	ra_[*]_col_ext [*] = – 'asc' for Ascending colon – 'desc' for descending colon – 'sig' for Sigmoid colon – 'trans' for transverse colon			Binary: Yes, no
For Ascending, descending, Sigmoid and transverse colon at W8 & 16 Normalization of wall-thickening		SOC Assessment, Intestinal Ultrasound	ra_[*]_col_norm [*] = – 'asc' for Ascending colon – 'desc' for descending colon – 'sig' for Sigmoid colon – 'trans' for transverse colon			Binary: Yes, no
Loss of stratification at W8 & 16		SOC Assessment, Intestinal Ultrasound	ra_loss_strat			Binary: Yes, no

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
Loss of colonic haustration at W8 & 16		SOC Assessment, Intestinal Ultrasound	ra_loss_col_haus			Binary: Yes, no
Structure formation at W8 & 16		SOC Assessment, Intestinal Ultrasound	ra_struct_form			Binary: Yes, no
Hyperechogenic reaction adjacent to the bowel wall		SOC Assessment, Intestinal Ultrasound	ra_hyper_react			Binary: Yes, no
Occurrence of new EIM at W8/W16 15 outcome/variables	Occurrence of EIM not reported at BL	Extra Intestinal Manifestations (EIM)	eim_cat eim_subcat eim_activity ('Past, but not active' vs. active at assessment)	-Categorical -Categorical - Binary	See section 4.3 for EIM improvement status at week_x (x can be equal to 8 or 16) Yes: EIM improvement status == New occurence	Binary: Yes, no
Number of EIMs at W8 and 16		Extra Intestinal Manifestations (EIM)			See section 4.3	Continuous
Number of comorbidities at W8 and 16		Extra Intestinal Manifestations (EIM)			See section 4.3	Continuous
PMS stool frequency subscore		PMS			See section 4.3	Continuous
PMS rectal bleeding subscore		PMS			See section 4.3	Continuous

Outcome	Definition	eCRF sheet	Variable	Variable type	Derivation	Outcome type
PMS physician's global assessment subscore		PMS			See section 4.3	Continuous

Table 7-b: EIM categories and subcategories

Variable	Category	Subcategory
Hepatobiliary; Primary sclerosing cholangitis	Hepatobiliary	Primary sclerosing cholangitis
Hepatobiliary; Cholangiocarcinoma		Cholangiocarcinoma
Hepatobiliary; Primary biliary cirrhosis		Primary biliary cirrhosis
Hepatobiliary; Autoimmune hepatitis		Autoimmune hepatitis
Hepatobiliary; Other		Other
Ocular; Uveitis	Ocular	Uveitis
Ocular; (Epi)scleritis		(Epi)scleritis
Ocular; Other		Other
Musculoskeletal; Inflammatory arthritis	Musculoskeletal	Inflammatory arthritis
Musculoskeletal; Other		Other
Mucocutaneous; Psoriasis	Mucocutaneous	Psoriasis
Mucocutaneous; Erythema nodosum		Erythema nodosum
Mucocutaneous; Pyoderma gangrenosum		Pyoderma gangrenosum
Mucocutaneous; Aphthous stomatitis		Aphthous stomatitis
Other; Other	Other	Other

7.2 Analysis methods

7.2.1 Primary analysis

In the primary analysis, all patients will be analyzed using the FAS set.

Proportions of patients achieving clinical, IBDQ and biochemical response and remission at W8 and W16 will be calculated and reported with the associated 95% Wilson confidence interval.

The course of continuous secondary outcomes (PMS, IBDQ score, PROs and fCAL) and of the exploratory additional PMS subscore outcomes over time will be depicted by box plots showing medians, quartiles, and outlying values. For these outcomes and for Medians and associated quartiles at baseline, W8, and W16 will be reported in a table.

For these outcomes, the change from baseline will be calculated at each time point as the observed value minus the value measured at baseline. The course of change over time, will be depicted by box plots showing medians, quartiles, and outlying values. Medians and associated quartiles at W8 and W16 will be reported in a table.

The course of fCAL over time will be shown separately for patients with and without clinical response as well as for patients with and without remission at W8 and W16. Medians and associated quartiles at W8 and W16 will be reported in a table.

Correlation between PRO outcomes and PMS, PMS subscores, IBDQ score and fCAL concentrations will be assessed at BL, W8 and W16 by the Spearman correlation coefficient. For each time point the correlation coefficient will be presented in a table.

Average daily dose of Tofacitinib during the trial, active UC and others additional outcomes assessed via ultrasound, number of comorbidities and EIM number, improvement, and new occurrence will be described at W8 and 16 in descriptive tables. Categorical variables will be summarized as number and proportion, continuous variables as median with quartiles range or mean with standard deviation, as appropriate.

7.2.2 Secondary analyses

If more than 2 patients are excluded from the on-tofacitinib analysis set (OTAS), all analysis described in the primary analysis section above will be conducted on the OTAS population.

7.2.3 Sensitivity analyses

Not applicable.

7.2.4 Subgroup analyses

Not applicable.

7.2.5 Additional analyses

Not applicable.

7.3 Interim analyses

Not applicable.

7.4 Missing data

Missing data will be ignored.

Rules for calculations of the different scores in the presence of missing information are detailed in the above sections.

7.5 Safety evaluation

Safety data are collected for the purpose of meeting routine pharmacovigilance reporting requirements. Safety data will not be analyzed, but number and frequency of (S)AEs will be reported, including tabulations by severity, number of withdrawals or does reductions due to AE, and by system organ class (SOC).

7.6 Subproject (if applicable)

Not applicable.

7.7 Statistical software

All the analysis will be done using R (version 3.6.0 or higher) [16].

7.8 Quality control

A second statistician will reproduce the primary analysis based on the exported data. If results deviate, the reason for the difference will be determined and a consensus must be reached.

8. Presentation of the results - Tables, Listings and Figures

8.1 Figures

8.1.1 Flow chart

See section 6.3.

8.1.2 Course of the PMS, PROs and fCAL concentration.

Figure (10 subplots): Boxplot showing the course of the PMS, PROs (each component separately) and fCAL concentration.
Figure (4 subplots): Boxplot (or line plot) showing the course of fCAL for patients with (subplot A) and without (subplot B) clinical response as well as for patients with (subplot C) and without (subplot D) remission at week 8 and 16.

8.2 Tables

8.2.1 Study participants

Baseline characteristics presented in the baseline table of this document (see section 6.4) will be presented in different tables presenting the:

table a. Key baseline characteristics including:
- Patient demographics,
- Concomitant medication at baseline,
- UC medication,
- Main UC disease characteristics,
- UC treatment history excluding prior exposure to oral & topical aminosalicylates, locally acting & systemic cortico-steroids (e.g. budesonide, prednisone), Thiopurines (e.g. AZA, 6-MP), Other immunosuppressants (e.g. cyclosporine, tacrolimus), TNF inhibitors (TNFi),
- fCAL at baseline,
- PRO at baseline,
- Co-morbidities

table b. EIMs
table c. SOC IUS

In each of these tables, categorical variables will be summarized as number and proportion, continuous variables as median with quartiles range or mean with standard deviation, as appropriate.

Prior exposure to oral & topical aminosalicylates, Locally acting & systemic corticosteroids (e.g. budesonide, prednisone), Thiopurines (e.g. AZA, 6-MP), Other immunosuppressants (e.g. cyclosporine, tacrolimus), TNF inhibitors (TNFi) will be presented as number and percentage in a separate table as below.

Table c: UC treatment history: Summary of primary reason for discontinuation of prior UC therapies by treatment group

Prior UC therapy, n (%)	Never prescribed	Lack of/ insufficient response	Loss of response	Intolerance/side effects	Unknown
Oral & topical aminosalicylates					

Prior UC therapy, n (%)	Never prescribed	Lack of/ insufficient response	Loss of response	Intolerance/side effects	Unknown
Localized/Topical corticosteroids (e.g. budesonide)					
Systemic corticosteroids (e.g. prednisone)					
Thiopurines (e.g. AZA, 6-MP)					
Other immunosuppressants (e.g. cyclosporine, tacrolimus)					
TNF inhibitors (TNFi)					
Vedolizumab					
Ustekinumab					

8.2.2 Efficacy Outcomes at W8 and W16

Legend:

	Primary outcome
	Secondary outcomes
	Exploratory outcomes

a. Main outcomes

Outcome	Proportion (%) of outcomes (n/N) [95% CI] *	
	W8	W16
Clinical response	*% (n/N) [CI]*	*% (n/N) [CI]*
Clinical remission	*% (n/N) [CI]*	*% (n/N) [CI]*
IBDQ response	*% (n/N) [CI]*	*% (n/N) [CI]*
IBDQ remission	*% (n/N) [CI]*	*% (n/N) [CI]*
Biochemical remission	*% (n/N) [CI]*	*% (n/N) [CI]*
FMS response	*% (n/N) [CI]*	*% (n/N) [CI]*
Remission	*% (n/N) [CI]*	*% (n/N) [CI]*
Mucosal healing	*% (n/N) [CI]*	*% (n/N) [CI]*
Response according to IUS assessment	*% (n/N) [CI]*	*% (n/N) [CI]*
Remission according to IUS assessment	*% (n/N) [CI]*	*% (n/N) [CI]*
Individual improvement in EIM	*% (n/N) [CI]*	*% (n/N) [CI]*
Categorical improvement in EIM	*% (n/N) [CI]*	*% (n/N) [CI]*

Footnotes:

* 95% Wilson confidence interval
Definitions for clinical response, clinical remission, IBDQ response, IBDQ remission, Biochemical remission, FMS response, remission, mucosal healing, response according to IUS assessment, remission according to IUS assessment, improvement in EIM.
**Results presented for each EIM and EIM category
*** Result presented for ascending colon, transverse colon, descending colon and sigmoid colon.

8.2.3 Temporal variation of PMS, PROs and fCAL concentration

Value and change from baseline at baseline, W8 and W16 of PMS, PROs (each component separately) and fCAL concentration (values presented as median and quartiles).

Outcome		Value at			Change from baseline at	
Category	Name	Baseline	W8	W16	W8	W16
PRO	Stool frequency	Median [Q1;Q3]	Median [Q1;Q3]	Median [Q1;Q3]	Median [Q1;Q3]	Median [Q1;Q3]
PRO	Rectal bleeding					
PRO	Urgency of defecation					
PRO	Abdominal pain					
PRO	Quality of sleep					
PRO	Daily fatigue					
PRO	Weekly fatigue					
PRO	Quality of life (IBDQ)					
PMS	PMS					
fCAL	fCAL concentration					

8.2.3.1 Temporal variation of the fcal concentration in patients with and without clinical response and remission

Value and change from baseline at baseline, W8 and W16 of fCAL concentration stratified by clinical outcomes at W8 and W16. (Values presented as median and quartiles)

Outcome	Value at			Change from baseline at	
	Baseline	W8	W16	W8	W16
fCAL all patients					
fCAL for patients with clinical response at W8					
fCAL for patients without clinical response W8					
fCAL for patients with clinical response at W16					

fCAL for patients without clinical response W16
fCAL for patients with clinical remission at W8
fCAL for patients without clinical remission W8
fCAL for patients with clinical remission at W16
fCAL for patients without clinical remission W16

Footnote: Definitions for clinical response and clinical remission according to IUS assessment.

8.3 Correlation between PRO and PMS, IBDQ score and fCAL concentrations outcomes.

Correlations measures (Spearman correlation coefficients) will be assessed at BL (Table a), W8 (Table b) and W16 (Table c). Results will be presented in similar but separated tables.

	Stool frequency	Rectal bleeding	Urgency of defecation	Abdominal pain	Quality of sleep	Daily fatigue	Weekly fatigue	Quality of life (IBDQ)	PMS	PMS sub-score1	PMS sub-score2	PMS sub-score3	fCAL
Stool frequency													
Rectal bleeding													
Urgency of defecation													
Abdominal pain													
Quality of sleep													
Daily fatigue													
Weekly fatigue													
Quality of life (IBDQ)													
PMS													
Stool frequency subscore of PMS													
Rectal bleeding subscore of PMS													
PGA subscore of PMS													
fCAL													

8.4 Additional exploratory outcomes

Additional exploratory outcomes listed in section 7.1 will be presented at W8 and 16 in separate descriptive tables. In each of these tables, categorical variables will be summarized as number and proportion, continuous variables as median with quartiles range or mean with standard deviation, as appropriate.

	W8	W16
Average daily dose of Tofacitinib during the trial	*median [Q1, Q3], or mean (sd)*	*median [Q1, Q3], or mean (sd)*
Active UC at W8 and 16 based on IUS assessments	*% (n/N) [CI]*	*% (n/N) [CI]*
Extension of wall-thickening*	*% (n/N) [CI]*	*% (n/N) [CI]*
Normalization of wall-thickening*	*% (n/N) [CI]*	*% (n/N) [CI]*
Loss of stratification	*% (n/N) [CI]*	*% (n/N) [CI]*
Loss of colonic haustration	*% (n/N) [CI]*	*% (n/N) [CI]*
Structure formation	*% (n/N) [CI]*	*% (n/N) [CI]*
Hyperechogenic reaction adjacent to the bowel wall	*% (n/N) [CI]*	*% (n/N) [CI]*
Occurrence of new EIM	*% (n/N) [CI]*	*% (n/N) [CI]*
Number of EIMs	*median [Q1, Q3], or mean (sd)*	*median [Q1, Q3], or mean (sd)*
Number of comorbidities	*median [Q1, Q3], or mean (sd)*	*median [Q1, Q3], or mean (sd)*
PMS stool frequency subscore	*median [Q1, Q3], or mean (sd)*	*median [Q1, Q3], or mean (sd)*
PMS rectal bleeding subscore	*median [Q1, Q3], or mean (sd)*	*median [Q1, Q3], or mean (sd)*
PMS physician's global assessment subscore	*median [Q1, Q3], or mean (sd)*	*median [Q1, Q3], or mean (sd)*

* For Ascending, descending, Sigmoid and transverse colon

8.5 Safety Data

8.5.1 Summary of AEs

	All Causalities	Treatment Related
Number of AEs		
Subjects with AEs [n (%)]		
Subjects with SAEs[a] [n (%)]		
Subjects with severe AEs[b] [n (%)]		
Subjects permanently withdrawn from tofocitinib due to AEs[c] [n (%)]		
Subjects with tofacitinib dose reduced or temporary discontinuation tofacitinib due to AEs [n (%)]		

Footnotes:
Included events from study database, even those that occurred after discontinuation of drug under study. Except for the number of AEs, subjects were counted only once per treatment in each row.
[a.] SAEs were determined according to the investigator's assessment.
[b.] Severity counts were based on the maximum severity or grade of events.
[c.] Discontinuation of tofacitinib due to AE based on the AE CRF is summarized, and numbers shown include subjects withdrawn for an AE of UC.

8.5.2 Severity of AEs, by system organ class and preferred term

System organ class Preferred Term	n (%)	Mild	Moderate	Severe
SOC 1				
PTi				
SOC 2				
PTi				
PTi+1				

9. Changes from the protocol

Table x: Changes from protocol

Header	Change	Reason
N patients	Sample size	Following Pfizer internal decision, recruitment was prematurely stopped after the enrollment of 18 patients.
Addition of new exploratory outcomes	- Average daily dose of Tofacitinib during the trial - Active UC at W8 and W16 - Normalization of wall-thickening, - Loss of stratification at W8 & W16, - Loss of colonic haustration at W8 & W16, - Structure formation at W8 & W16, - Hyperechogenic reaction adjacent to the bowel wall, - Occurrence of new EIM at W8/W16, - Number of EIMs at W8 and W16, - Number of comorbidities at W8 and W16, - PMS stool frequency subscore, - PMS rectal bleeding subscore, - PMS physician's global assessment subscore	Sponsor decision
PPset	No analysis will be conducted on the PPset	Only 18 patients were recruited
Secondary analysis	- The effect of participants' baseline characteristics on change in PMS, PROs and fCAL values will not be assessed - subgroup analysis will not be conducted	Only 18 patients were recruited

10. References

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