STATISTICAL ANALYSIS PLAN

NCT Number: NCT04876690

Study Title: Quality of Life of Crohn's Disease Patients With Complex Perianal Fistulas: an Observational, Cross-sectional Study

Study Number: IBD-5007

SAP Version and Date:

Version 1.0: 04-May-2022

IBD-5007 - Quality of life of Crohn's disease patients with complex perianal fistulas: an observational, cross-sectional study (CONFLICT)

Statistical Analysis Plan

Version 1.0, 04 May 2022

Prepared by:

CTI Clinical Trial & Consulting Services

Rua Tierno Galvan, Torre 3, Piso 16

1070-274 Lisboa

Portugal

Requested by:

Takeda Farmacêuticos Portugal

Quinta da Fonte, Rua dos Malhões nº5,

Edifício Q56 D. Pedro I, Piso 3

Paço de Arcos

2770-071, Lisboa

Portugal

TITLE PAGE

Study title:	Quality of life of Crohn's disease patients with complex perianal fistulas: an observational, cross-sectional study (CONFLICT)
Study code:	IBD-5007
Study type:	Observational
Study drug	Not applicable
Therapeutic area:	Crohn's disease
Sponsor:	Takeda Farmacêuticos Portugal Quinta da Fonte, Rua dos Malhões nº5, Edifício Q56 D. Pedro I, Piso 3 Paço de Arcos 2770-071, Lisboa Portugal
Version #, date:	Version 1.0, 04 May 2022
Statistical analysis plan performed by:	CTI Clinical Trial & Consulting Services Rua Tierno Galvan, Torre 3, Piso 16 1070-274 Lisboa Portugal

SIGNATURE PAGE

STUDY TITLE: Quality of life of Crohn's disease patients with complex perianal fistulas: an observational, cross-sectional study (CONFLICT)

PROTOCOL VERSION: Version 1.0

PROTOCOL DATE: 25Feb2021

SAP PREPARED BY:

DocuSigned by:
[redacted]

[redacted]
[redacted]
CTI Clinical Trial & Consulting Services

SAP REVIEWED BY:

DocuSigned by:
[redacted]

[redacted]
[redacted] - Biometrics
CTI Clinical Trial & Consulting Services

SAP REVIEWED AND APPROVED BY:

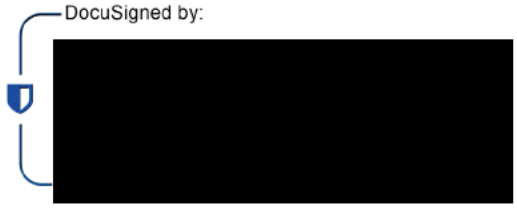
DocuSigned by:

[redacted]

[redacted] RWE department

Takeda Farmacêuticos Portugal

DocuSigned by:



[redacted]

[redacted]

Takeda Farmacêuticos Portugal

Note that the last signature date is the effective date of the plan.

REVISION LOG

Version No.	Version Date	Author	Changes from Previous Approved Versions
1.0	04May2022	[redacted]	Not Applicable (First Version)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Drug
BMI	Body max index
CD	Crohn's Disease
CPF	Complex Perianal Fistula
CRF	Clinical report form
CRO	Contract Research Organization
eCRF	Electronic clinical report form
GPP	Good Pharmacoepidemiology Practices
HBI	Harvey Bradshaw Index
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
ICU	Intensive Care Unit
IECs	Independent Ethics Committees
MCS-12	Mental composite score
NIS	Non-Interventional Study
PCS-12	Physical composite score
Q1	1st Quartile
Q3	3rd Quartile
QoL	Quality of Life
RWE	Real World Evidence
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SIBDQ	Short IBDQ
SOC	System organ class
SOP	Standard operating procedure
SQOL-F	Sexual Quality of Life - Female
SQOL-M	Sexual Quality of Life - Male
TLFs	Tables, Listings and Figures
WPAI	Work Productivity and Activity Impairment

TABLE OF CONTENTS

1 RATIONALE

This Statistical Analysis Plan (SAP) was written in accordance with CTI standard operating procedure (SOP) GL-RWE-BIO-001 on Biostatistics for RWE Studies and intends to provide guidelines from which the analysis will proceed, create a common and clear understanding of the planned analysis by all involved, clarify issues which was not clarified in the protocol, expand statistical section of the protocol, provide basis for the statistical section of the statistical report and reduce the opportunity for bias by prospectively defining analysis. This SAP was prepared by the biostatistician who will be further responsible (if possible) for the statistical analysis of the study data.

This SAP, in particular table shells and examples of figures/graphs, was reviewed and approved by the Sponsor's Representative previously to database locking and performance of the statistical analysis.

Any changes to the planned statistical methodology here defined during the statistical analysis of the study data will be documented in the Statistical Report and in the Study Clinical Report.

This document was written in accordance with the information contained in the Study Protocol IBD-5007, version 1.0, of 25 February 2021 and CRF Version 2.0, 16 April 2021.

2 STUDY OBJECTIVES AND ENDPOINTS

The aim of this study is to characterize the Quality of Life [QoL - general and IBD (Inflammatory Bowel Disease)-specific], sexual function, work productivity and activity impairment, and healthcare resource utilization among Crohn's Disease (CD) patients with Complex Perianal Fistula (CPFs) attending secondary care services (gastroenterology appointments) in Portugal.

2.1 Objectives

2.1.1 Primary objective

1) To assess the general QoL among CD patients with CPFs attending secondary care services in Portugal.

2.1.2 Secondary objectives

1) To assess the IBD-specific QoL among CD patients with CPFs.
2) To assess the sexual function among CD patients with CPFs.

3) To assess fecal incontinence among CD patients with CPFs.
4) To assess the work productivity and activity impairment among CD patients with CPFs.
5) To assess the healthcare resource utilization in CD patients with CPFs within the three years prior to the inclusion visit.
6) To describe the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.
7) To describe the pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
8) To explore the association between general QoL and the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.

2.1.3 Exploratory objectives

1) To explore the association between IBD-specific QoL/sexual function and the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.

2.2 Endpoints

2.2.1 Primary endpoints

1) Meta-scores of the SF-12 questionnaire (physical composite score [PCS-12] and mental composite score [MCS-12]).

2.2.2 Secondary endpoints

1) Short IBDQ (SIBDQ) questionnaire score.
2) SQOL-M and SQOL-F questionnaire scores for male and female patients, respectively.
3) Wexner score.
4) Work Productivity and Activity Impairment (WPAI) questionnaire score.
5) Outpatient visits (gastroenterology or other medical specialty), emergency room visits, hospitalizations (≥24 hours), and pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
6) Patients' sociodemographic, anthropometric and clinical characteristics.
7) Pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
8) Association between general QoL (PCS-12 and MCS-12) and the patients' socio-demographic, anthropometric and clinical characteristics.

2.2.3 Exploratory endpoints

1) Association between IBD-specific QoL (SIBDQ score)/sexual function (SQOL-M and SQOL-F scores) and the patients' socio-demographic, anthropometric and clinical characteristics.

3 STUDY DESIGN

This is a national, observational, cross-sectional study primarily aimed at assessing the general QoL among CD patients with CPFs in the Portuguese routine clinical practice. In addition to the cross-sectional design, the study will have a retrospective component to collect data on healthcare resource utilization and on the pharmacological and surgical treatments used for the management of CPFs in the three years prior to the inclusion visit.

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

- The assignment of a patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the patients.
- Epidemiological methods shall be used for the analysis of collected data.

The study will be conducted in five Portuguese public hospitals experienced in the management of patients with CD. Gastroenterologists working at the participating hospitals will participate in the study as investigators.

4 STUDY POPULATION

4.1 Inclusion Criteria

1) Male or female patients aged 18 years or older at the inclusion visit.
2) Patients diagnosed with CD.
3) Presence of CPF(s), defined as ≥1 of the following criteria:
    a. high intersphincteric, high transsphincteric, extrasphincteric, or suprasphincteric location;
    b. ≥ 2 external openings;
    c. associated collections.
4) Patients attending routine gastroenterology appointments at the participating hospitals.
5) Patients capable of understanding and complying with protocol requirements, in the investigator's opinion.

6) Patients or, when applicable, the patients' legally acceptable representative, who signed and dated a written informed consent form and any required privacy authorization prior to the initiation of any study procedures.

4.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for study inclusion:

1) Patients diagnosed with ulcerative colitis or indeterminate IBD.
2) Patients with non-complex fistulas or with fistulas types other than perianal (e.g., rectovaginal).
3) Patients currently participating in any interventional clinical trial.

Patients should be included in the study only once.

Data erroneously collected from patients for whom written consent is not available, will not be included in or will be deleted from the database.

5 PROTOCOL CLARIFICATIONS

Some clarifications/alterations regarding the protocol:

In section 10 is presented new derived variables and variables transformations that will be used during the statistical programming.

Descriptive statistics for quantitative variables will also present quartiles values (Q1 and Q3) summarized using descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values), interquartile range and.

The exploratory analysis of the association between independent variables of interest and sexual function questionnaires will be performed separately by gender (SQOL-M score for male patients and SQOL-F for female patient), therefore two linear multiple regression models will be performed.

The linear multiple regression models will only be applicable if the sample size is appropriate for the model modulation.

For the factors associated with general QoL (SF-12) and IBD-specific QoL (SIBDQ score) the independent variables of interest, sexual function scores (SQOL-M and SQOL-F scores), were standardized accordingly to the formula presented in section 10. This standardized variable allows to enter the data of the sexual function scores for both genders (male and female) in the same variable, avoiding performing two separated linear regression models for SF-12 scores for each gender

6 DEFINITION OF ANALYSIS SUBSETS

One dataset will be defined for the study, eligible dataset.

Analysis dataset will include all patients who sign an Informed consent form (ICF), who fulfil the selection criteria presented in section 4.

7 RATIONALE AND CALCULATION OF THE SAMPLE SIZE

The sample size was determined based on the study's primary objective – to assess the general QoL of CD patients with CPF.

To determine the sample size, an expected standard deviation (SD) of the outcome (SF-12 score) is required. Ideally, a SD of the SF-12 score assessed in CD patients with CPFs should be used. However, we found no studies in the literature reporting SF-12 scores exclusively for CD patients with CPFs. Alternatively, we used the data reported by a study that evaluated the QoL via SF-12 in CD patients (2). This study reported mean scores of 49.1 (± 10.2) and 49.6 (± 10.6) for PCS-12 and MCS-12, respectively.

Considering an expected SD of 10.6 (the most conservative) based on the abovementioned study, a confidence level at 95% and a margin of error of approximately 2.3, a total of 80 patients should be included in the study to assess the general QoL via the SF-12 questionnaire. The formula below was used for the sample size determination:

$$n = \frac{z^2 \times s^2}{m^2}$$

Where:

n = required sample size

z = confidence level at 95% (SD of 1.96)

s = expected standard deviation

m = margin of error

8 STATISTICAL HYPOTHESIS

This is a descriptive study and for this reason, no hypothesis were planned for this study.

9 STATISTICAL METHODS

All quantitative variables will be summarized using descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values), interquartile range and

quartiles values (Q1 and Q3). All qualitative variables will be summarized by absolute (n) and relative (%) frequencies. Percentages will be calculated based on non-missing values. The statistical analysis will be performed through frequency tables for qualitative variables and tables with descriptive statistics for quantitative variables.

There will be no imputation of missing data for this study, unless otherwise specified.

Dates may be entered into the database with day, month, and/or year given as "unknown." Dates will only be imputed when needed. The planned imputation method is as follows:

- Missing year: no imputation
- Missing month: Month = July
- Missing day: day = 15
- Missing month/day: Month/day = July 1st

When a date imputation results in a negative time or in an inconsistent date the new variable time difference will be considered as missing (e.g. start date 16-Jul-2019 and stop date UNK-Jul-2019 – with data imputation, stop date would be 15-Jul-2019, before the start date and time difference will be -1 days).

Data analysis will be performed using SAS® (version 9.4; SAS Institute Inc, Cary, USA).

9.1 Primary analysis

To characterize the patients' general QoL, the results obtained for each item of the SF-12 will be summarized in a frequency table, including counts (n) and percentages (%). The two resulting meta-scores – the physical health composite scale score and the mental health composite scale score – will be summarized by descriptive statistics, namely mean (with 95% CI), SD, median, range (minimum and maximum values), interquartile ranges and quartiles values (Q1 and Q3).

Ninety-five per cent CIs will be determined for the mean meta-scores of the SF-12 according to the following formula:

$$mean \pm 1.96 \times \frac{standard\ deviation}{\sqrt{n}}$$

9.2 Secondary analysis

9.2.1 IBD-specific QoL

To characterize the patients' IBD-specific QoL, the results obtained for each item of the SIBDQ and the overall score will be summarized by descriptive statistics, namely mean, SD, median, range (minimum and maximum values), interquartile ranges and quartiles values (Q1 and Q3).

9.2.2 Sexual function

The results obtained for each of the 11 items included in the SQOL-M questionnaire (for male patients) will be summarized in a frequency table, including counts (n) and percentages (%), and by descriptive statistics, namely mean, SD, median, range (minimum and maximum values), interquartile ranges and quartiles values (Q1 and Q3). The overall score will also be summarized descriptively.

The results obtained in each of the 18 items included in the SQOL-F (for female patients) will be summarized in a frequency table, including counts (n) and percentages (%), and by descriptive statistics, namely mean, SD, median, range (minimum and maximum values), interquartile ranges and quartiles values (Q1 and Q3). The overall score will also be summarized descriptively.

9.2.3 Fecal incontinence

The results obtained for each of the five items of the Wexner score will be summarized in a frequency table, including counts (n) and percentages (%). The overall score will be summarized by descriptive statistics, namely mean, SD, median, range (minimum and maximum values), interquartile ranges and quartiles values (Q1 and Q3).

9.2.4 Impact on social/work activities and work productivity

Results from the first question of the WPAI will be summarized by counts (n) and percentages (%). Data on the remaining six questions will be summarized by descriptive statistics, namely mean, SD, median, range (minimum and maximum values), interquartile ranges and quartiles values (Q1 and Q3). Moreover, the scores obtained for the four domains assessed by the WPAI – absenteeism (work time missed), presenteeism (impairment at work / reduced on-the-job effectiveness), work productivity loss and activity impairment – will be summarized descriptively.

9.2.5 Healthcare Resource Utilization

Data on outpatient visits (number, medical specialty), emergency room visits (number), hospitalizations ≥24 hours (number, length of stay, ICU admission, ICU length of stay), and pharmacological and surgical treatments used for CPF management (number) within the three years prior to the inclusion visit will be summarized descriptive statistics – namely mean, SD, median, range (minimum and maximum), interquartile ranges and quartiles values (Q1 and Q3) – or by absolute (n) and relative (%) frequencies, as applicable.

Moreover, the number of patients with at least one outpatient visit, emergency room visit, and hospitalization ≥24 hours will be presented.

9.2.6 Patients' characteristics

All patients sociodemographic, anthropometric and clinical characteristics described in Section 4.6 of the protocol will be summarized by descriptive statistics – namely mean, SD, median, range (minimum and maximum), interquartile ranges and quartiles values (Q1 and Q3) – or by absolute (n) and relative (%) frequencies, as applicable. The classification of patients as treatment- and/or surgery-naïve will also be presented by descriptive statistics.

Patients will be divided into three categories based on the timing of CPF diagnosis in relation to the CD diagnosis:

- Prior to CD diagnosis
- At CD presentation (i.e., when CPF was diagnosed in the same year as CD)
- During the course of the disease

Based on the Harvey Bradshaw Index (HBI) score, patients will be categorized into four categories:

- Remission (score <5)
- Mild activity (5-7)
- Moderate activity (8-16)
- Severe activity (>16)

Based on the Perianal Disease Activity Index (PDAI) score, patients will be divided into two groups (1):

- Inactive fistulizing disease (≤4)
- Active fistulizing disease (>4)

9.2.7 Pharmacological treatments and surgeries for CPF

The pharmacological and surgical treatments used for the management of CPF (see Section 4.6 of the protocol) will be described by counts (n) and percentages (%).

For each pharmacological treatment (antibiotics, monoclonal antibodies and immunosuppressants), patients will be divided into three categories (current users, past users, and non-users) considering the three years prior to the inclusion visit. For instance, for immunosuppressants, the proportions of patients using these drugs at the inclusion visit, those who have used them within the last three years, and those who have not used them in this period will be summarized.

Current combinations (i.e., combinations used by the patient at the inclusion visit) will be described by counts (n) and percentages (%).

9.2.8 Factors associated with general QoL (SF-12)

9.2.8.1 Bivariate analysis

Comparisons of general QoL (for the two SF-12 meta-scores – PCS-12 and MCS-12) and between groups defined based on qualitative variables, of patient characteristics, will be tested with the t-test for independent samples/ANOVA for two/three or more independent samples or with the Mann-Whitney/Kruskal-Wallis non-parametric tests, according to the assumption validations of the statistical test. The following qualitative variables will be considered for the bivariate analysis: sex, smoking status, employment status, extraintestinal manifestations of Crohn's disease, Montreal classification for CD disease (age at onset, disease location, and disease behavior), fistula type and position, CD disease activity (remission, mild activity, moderate activity, and severe activity), treatment-naïve (yes/no), surgery-naïve (yes/no), treatment- and surgery-naïve (yes/no), surgery for the management of CPFs within the three years prior to the inclusion visit (yes/no), type of surgery, and presence of seton, perianal abscess and anorectal stricture.

Associations between general QoL (for PCS-12 and MCS-12) and quantitative variables of patient characteristics, will be performed through Pearson correlation coefficient or Spearman correlation coefficient (in case the normality assumption is not verified). The following quantitative variables will be considered for the bivariate analysis: age, body max index (BMI), time since CD diagnosis, number of CPFs presented at the inclusion visit, time since CPF diagnosis (in patients with more than one CPF at the inclusion visit, the oldest date of diagnosis will be considered), PDAI score, number of internal and external fistula openings, time since seton placement, SIBDQ score, SQOL-M score (for male patients) and SQOL-F score (for female patients), and Wexner score.

9.2.8.2 Linear multiple regressions

Moreover, linear multiple regressions will be used to explore the association between the dependent variable (PCS and MCS meta-scores of the SF-12) and independent variables of interest according to the bivariate analysis results. Regression coefficients (B) and 95% confidence intervals will be computed to measure the magnitude of these associations.

9.2.9 Exploratory analyses

The same methodology described in Section 9.2.8 (for factors associated with general QoL [SF-12]) will be followed to explore the association between independent variables of interest and the following dependent variables:

- IBD-specific QoL (SIBDQ score)

- Sexual function (SQOL-M and SQOL-F scores for male and female patients, respectively)

10 DATA, DERIVATIONS AND TRANSFORMATIONS

Analysis dataset - A dichotomous variable will be calculated:

Yes – Patients who meet all inclusion criteria, not meet any of the exclusion criteria, sign the informed consent.

No – Otherwise.

If any of the previous variables were not available, then this new variable will be considered as missing information.

BMI categories - A categorical variable will be calculated (3):

Underweight – Patients with BMI <18.50 kg/m^2

Normal range – Patients with BMI between 18.50 and 24.99 kg/m^2

Overweight – Patients with BMI between 25.00 and 29.99 kg/m^2

Obese – Patients with BMI ≥ 30.00 kg/m^2

Patients with missing information of BMI will be considered as a missing value in this new derived variable.

Time between CD diagnosis date and date of study visit (months) – Difference between date of study visit and CD diagnosis date + 1 day, in days and divide by 30.5 so it will be converted to months.

$$Time\ between\ CD\ diagnosis\ date\ and\ date\ of\ study\ visit\ (months) = \frac{study\ visit\ date - \ CD\ diagnosis\ date\ + 1\ (days)}{30.5}$$

If any date used for the calculation of this new variable is complete missing, then this new variable will be considered as missing information. In case of incomplete missing dates, the data imputation presented in section 9 will be used. In case of inconsistency dates after imputation methods (e.g. study visit date previous to CD diagnosis date) this new variable will be considered as missing information.

Total number of fistulas per patient - sum of fistulas reported in the eCRF, by each patient.

Time between diagnosis date of first CPF and date of visit (months) – Difference between date of study visit and first CPF diagnosis date + 1 day, in days and divide by 30.5 so it will be converted to months.

$$Time\ between\ diagnosis\ date\ of\ first\ CPF\ and\ date\ of\ visit\ \ (months) = \frac{study\ visit\ date - \ first\ CPF\ diagnosis\ date\ + 1\ (days)}{30.5}$$

If any date used for the calculation of this new variable is complete missing, then this new variable will be considered as missing information. In case of incomplete missing dates, the data imputation presented in section 9 will be used. In case of inconsistency dates after imputation methods (e.g. study visit date previous to first CPF diagnosis date) this new variable will be considered as missing information.

Presence of perianal abscess - A dichotomous variable will be calculated:

Yes – If the patient reported perianal abscess as other perianal lesion besides CPF.
No – If the patient did not reported perianal abscess as other perianal lesion besides CPF or any other type of perianal lesion.

Patients with missing information of other perianal lesion will be considered as a missing value in this new derived variable.

Presence of anorectal stricture - A dichotomous variable will be calculated:

Yes – If the patient reported anorectal stricture as other perianal lesion besides CPF.
No – If the patient did not reported anorectal stricture as other perianal lesion besides CPF or any other type of perianal lesion.

Patients with missing information of other perianal lesion will be considered as a missing value in this new derived variable.

Number of internal fistula openings per patient - sum of internal fistulas openings reported in the eCRF, by each patient.

Number of external fistula openings per patient - sum of external fistulas openings reported in the eCRF, by each patient.

Fistula with high intersphincteric type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with high intersphincteric type.
No – Patient who did not report any CPFs with high intersphincteric type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with high transsphincteric type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with high transsphincteric type.

No – Patient who did not report any CPFs with high transsphincteric type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with suprasphincteric type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with suprasphincteric type.

No – Patient who did not report any CPFs with suprasphincteric type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with extrasphincteric type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with extrasphincteric type.

No – Patient who did not report any CPFs with extrasphincteric type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with superficial type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with superficial type.

No – Patient who did not report any CPFs with superficial type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with low intersphincteric type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with low intersphincteric type.

No – Patient who did not report any CPFs with low intersphincteric type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with low transsphincteric type - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with low transsphincteric type.

No – Patient who did not report any CPFs with low transsphincteric type.

If the variable fistula type is missing for any CPF, then this new variable will be considered as missing information.

Fistula with midline position - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with midline position.

No – Patient who did not report any CPFs with midline position.

If the variable fistula position is missing for any CPF, then this new variable will be considered as missing information.

Fistula with lateral position - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with lateral position.

No – Patient who did not report any CPFs with lateral position.

If the variable fistula position is missing for any CPF, then this new variable will be considered as missing information.

Fistula with seton - A dichotomous variable will be calculated:

Yes – Patients who reported at least one CPF with seton.

No – Patient who did not report any CPFs with seton.

If the variable presence of seton is missing for any CPF, then this new variable will be considered as missing information.

Treatment and surgery-naïve - A dichotomous variable will be calculated:

Yes – Patients who reported to be treatment AND surgery naïve simultaneously.

No – Patient who reported to be only treatment OR only surgery naïve, or if did not reported to be treatment and surgery naïve.

If any of the previous variables were not available, then this new variable will be considered as missing information.

Time since seton placement (months) – Difference between date of study visit and first seton surgery (Cutting seton or Loose seton) reported + 1 day, in days and divide by 30.5 so it will be converted to months.

$$Time\ since\ seton\ placement\ \ (months) = \frac{study\ visit\ date - \ first\ seton\ surgery\ date\ + 1\ (days)}{30.5}$$

Surgery fistulotomy - A dichotomous variable will be calculated:

Yes – Patients who reported fistulotomy as a type of surgery.

No – Patient who did not reported fistulotomy as a type of surgery or did not reported any type of surgery.

Surgery advancement flap - A dichotomous variable will be calculated:

Yes – Patients who reported advancement flap as a type of surgery.

No – Patient who did not reported advancement flap as a type of surgery or did not reported any type of surgery.

Surgery ligation of the intersphincteric fistula tract (LIFT)- A dichotomous variable will be calculated:

Yes – Patients who reported ligation of the intersphincteric fistula tract (LIFT) as a type of surgery.

No – Patient who did not reported ligation of the intersphincteric fistula tract (LIFT) as a type of surgery or did not reported any type of surgery.

Surgery fibrin glue - A dichotomous variable will be calculated:

Yes – Patients who reported fibrin glue as a type of surgery.

No – Patient who did not reported fibrin glue as a type of surgery or did not reported any type of surgery.

Surgery anal fistula plug - A dichotomous variable will be calculated:

Yes – Patients who reported anal fistula plug as a type of surgery.

No – Patient who did not reported anal fistula plug as a type of surgery or did not reported any type of surgery.

Surgery defunctioning stoma - A dichotomous variable will be calculated:

Yes – Patients who reported defunctioning stoma as a type of surgery.

No – Patient who did not reported defunctioning stoma as a type of surgery or did not reported any type of surgery.

Surgery cutting seton - A dichotomous variable will be calculated:

Yes – Patients who reported cutting seton as a type of surgery.

No – Patient who did not reported cutting seton as a type of surgery or did not reported any type of surgery.

Surgery loose seton - A dichotomous variable will be calculated:

Yes – Patients who reported loose seton as a type of surgery.

No – Patient who did not reported loose seton as a type of surgery or did not reported any type of surgery.

Surgery other - A dichotomous variable will be calculated:

Yes – Patients who reported other as a type of surgery.

No – Patient who did not reported other as a type of surgery or did not reported any type of surgery.

Length of stay (days) – Difference between discharge date and admission date + 1 day, in days.

$$Length\ of\ stay\ \ = discharge\ date - \ admission\ date\ + 1\ (days)$$

For hospitalization without discharge date, length of stay will not be calculated.

If any date for the calculation of length of stay is complete missing, that hospitalization will not be considered for the calculation of length of stay and will be considered as missing information. In case of incomplete missing dates, the data imputation presented in section 9 will be used.

Patient hospitalized (≥24 hours) in the ICU due to CPF in the last three years - A dichotomous variable will be calculated:

Yes – Patients who reported at least one hospitalization with ICU admission.
No – Patients without any reported hospitalization with ICU admission.

Patients with missing information for the question of "Was the patient hospitalized (≥24 hours) due to CPF in the last three years?" or "Intensive Care Unit admission?" in the eCRF will be considered as a missing value in this new derived variable.

Number of hospitalizations per patient - sum of all hospitalizations reported in the eCRF, by each patient.

Number of ICU hospitalizations per patient - sum of all ICU hospitalizations reported in the eCRF, by each patient.

Patient with CPFs categories - A categorical variable will be calculated:

Patients with CPFs prior to CD diagnosis – Patients with at least one CPF diagnosed before the CD diagnosis date.
Patients with CPFs at CD presentation – Patients with at least one CPF diagnosed in the same year of the CD diagnosis, but after the diagnosis date and without any CPF diagnosed before the CD diagnosis date.
Patients with CPFs during the course of the disease - Patients with at least one CPF diagnosed after the year of CD diagnosis and without any CPF diagnosed before the date of CD diagnosis or in the year of CD diagnosis.

If any date of CD diagnosis or CPF diagnosis is complete missing, then this new variable will be considered as missing information. In case of incomplete missing dates, the data imputation presented in section 9 will be used. In cases where the patient has at least two CPFs with one of them with complete missing diagnosis date then this new variable will be considered as missing information.

Harvey Bradshaw Index (HBI) categories - A categorical variable will be calculated:

Remission – Patients with HBI score less than 5 points (HBI score < 5).

Mild activity – Patients with HBI score between 5 and 7 points (5 ≤ HBI score ≤ 7).

Moderate activity – Patients with HBI score between 8 and 16 points (8 ≤ HBI score ≤16).

Severe activity – Patients with HBI score greater than 16 points (HBI score >16).

Patients with missing HBI score will be considered as a missing value in this new derived variable.

Perianal Disease Activity Index (PDAI) categories - A dichotomous variable will be calculated:

Inactive fistulizing disease – Patients with PDAI score less or equal than 4 points (PDAI score ≤ 4).

Active fistulizing disease – Patients with PDAI score greater than 4 points (PDAI score > 4).

Patients with missing PDAI score will be considered as a missing value in this new derived variable.

Current pharmacological treatment - A dichotomous variable will be calculated:

Yes – Patients who **reported at least one** pharmacological treatment *i* or subclass treatment *j* **ongoing** at visit date.

No – Patients who **did not reported any** pharmacological treatment *i* or subclass treatment *j* **ongoing** at visit date.

$$i = \{\text{Antibiotics, Monoclonal antibodies, Immunosuppressants, Other }\}$$

$$j = \{\begin{array}{c}\text{Ciprofloxacin, Metronidazole, Other antibiotic, Infliximab, Adalimumab, Ustekinumab,} \\ \text{Vedolizumab, Other monoclonal antibody, Azathioprine, Mercaptopurine,} \\ \text{Other Immunosuppressants and Other pharmacological treatment}\end{array}\}$$

Past users of pharmacological treatment - A dichotomous variable will be calculated:

Yes – Patients who **reported at least one** pharmacological treatment *i* or subclass treatment *j* **not ongoing** at visit date.

No – Patients who **did not reported any** pharmacological treatment *i* or subclass treatment *j* **not ongoing** at visit date.

$$i = \{\text{Antibiotics, Monoclonal antibodies, Immunosuppressants, Other }\}$$

$$j = \{ \begin{matrix} \text{Ciprofloxacin, Metronidazole, Other antibiotic, Infliximab, Adalimumab, Ustekinumab,} \\ \text{Vedolizumab, Other monoclonal antibody, Azathioprine, Mercaptopurine,} \\ \text{Other Immunosuppressants and Other pharmacological treatment} \end{matrix} \}$$

Current pharmacological treatment user combination - A dichotomous variable will be calculated:

Combination pharmacological treatment – Patients who reported at least one pharmacological treatment from two different treatment subclasses (antibiotics, monoclonal antibodies, immunosuppressants and other treatment).

Single pharmacological therapy – Patients who did not reported any current pharmacological treatment or who report only one or several pharmacological treatment from the same subclass. (antibiotics, monoclonal antibodies, immunosuppressants and other treatment).

Current pharmacological treatment user combinations treatments - A categorical variable will be calculated:

Antibiotics and Monoclonal antibodies – If a patient reported only antibiotic and monoclonal antibodies treatment as an ongoing pharmacological treatment at visit date.

Antibiotics and Immunosuppressants – If a patient reported only antibiotic and immunosuppressants treatment as an ongoing pharmacological treatment at visit date.

Antibiotics and Other – If a patient reported only antibiotic and other treatment as an ongoing pharmacological treatment at visit date.

Antibiotics and Monoclonal antibodies and Other – If a patient reported only antibiotic, monoclonal antibodies and other treatment as an ongoing pharmacological treatment at visit date.

All the pharmacological treatments combinations will be added during the statistical analysis.

Non-pharmacological treatment user - A dichotomous variable will be calculated:

Yes – Patients who did not report any pharmacological treatment of the *i* class.

No – If a patient reported at least one pharmacological treatment of the *i* class.

$$i = \{\text{Antibiotics, Monoclonal antibodies, Immunosuppressants, Other }\}$$

WPAI score: Percent work time missed due to health problems – The following formula must be considered, considering WPAI questionnaire:

$$[\frac{Q2}{(Q2+Q4)}] \times 100$$

WPAI score: Percent impairment while working due to health problems – The following formula must be considered, considering WPAI questionnaire:

$$(\frac{Q5}{10}) \times 100$$

WPAI score: Percent overall work impairment due to health problems – The following formula must be considered, considering WPAI questionnaire:

$$\{\frac{Q2}{(Q2+Q4)} + [(1-(\frac{Q2}{(Q2+Q4)})) \times (\frac{Q5}{10})]\} \times 100$$

WPAI score: Percent activity impairment due to health problems – The following formula must be considered, considering WPAI questionnaire:

$$(\frac{Q6}{10}) \times 100$$

Physical composite score (assessed by SF-12) – Will be calculated using the PRO CoRE software by QualityMetric.

Mental composite score (assessed by SF-12) – Will be calculated using the PRO CoRE software by QualityMetric.

SQoL-M score – sum of 11 items with a total score ranging from 11 to 66. Each item is scored using a 6-point Likert-type scale ranging from 1 as completely agree to 6 as completely disagree.

SQoL-F score – sum of 18 items with a total score ranging from 18 to 108. Each item is scored using a 6-point Likert-type scale ranging from 1 as completely agree to 6 as completely disagree.

SQoL score standardized (percentual value) – The following formula must be considered, considering WPAI questionnaire:

If male, $\text{SQoL score standardized} = \frac{\textbf{SQoL–M score} \times 100}{66}\%$

If female, $\text{SQoL score standardized} = \frac{\textbf{SQoL–M score} \times 100}{108}\%$

11 REFERENCES

(1). Rencz F, Stalmeier PFM, Péntek M, Brodszky V, Ruzsa G, Gönczi L, et al. Patient and general population values for luminal and perianal fistulising Crohn's disease health states. Eur J Health Econ HEPAC Health Econ Prev Care. 2019 Jun;20(Suppl 1):91–100.

(2). Christiansen LK, Lo B, Bendtsen F, Vind I, Vester-Andersen MK, Burisch J. Health-related quality of life in inflammatory bowel disease in a Danish population-based inception cohort. United Eur Gastroenterol J. 2019 Aug;7(7):942–54.

(3) World Health Organization. Body mass index - BMI. [accessed on 28 Jan 2022]. Available at: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

12 APPENDIX

External document: CONFLICT - TLFs shell Version 1.0, 04May2022

DocuSign

Certificate Of Completion

Envelope Id: 07F45F21A5094D74998A49689BC0AFD3
Status: Completed
Subject: Please DocuSign: CONFLICT - SAP Version 1.0 04May2022.docx
Source Envelope:
Document Pages: 28 Signatures: 4
Certificate Pages: 6 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Envelope Originator:
[redacted]
100 E. RiverCenter Blvd
Suite 1600
Covington, KY 41011
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
5/4/2022 5:40:22 AM

Holder: [redacted]

Location: DocuSign

Signer Events	Signature	Timestamp
[redacted], Biometrics CTI Clinical Trial and Consulting Services Security Level: Email, Account Authentication (Required)	[redacted]	

With Signing Authentication via DocuSign password
With Signing Reasons (on each tab):
I have reviewed this document

Electronic Record and Signature Disclosure:
Accepted: 8/24/2020 6:12:50 AM
ID: 90649e32-e4da-4f10-b084-47b8ea21bec4

[redacted] Disease Area [redacted], RareHem & PDT Takeda Pharmaceuticals - Default Security Level: Email, Account Authentication (Required)	[redacted]	

With Signing Authentication via DocuSign password
With Signing Reasons (on each tab):
Aprovo este documento

Electronic Record and Signature Disclosure:
Accepted: 11/17/2020 9:23:06 AM
ID: 1c151a75-c38a-4945-b155-8efacd5afe29

Signer Events	Signature	Timestamp
[redacted] CTI Clinical Trial and Consulting Services Security Level: Email, Account Authentication (Required)	[redacted]	

With Signing Authentication via DocuSign password
With Signing Reasons (on each tab):
I am the author of this document

Electronic Record and Signature Disclosure:
Accepted: 10/23/2020 4:58:23 AM
ID: 269c917a-2bc5-408b-a779-ad5b04ea4c4a

[redacted] Takeda Pharmaceuticals - Default Security Level: Email, Account Authentication (Required)	[redacted]	

With Signing Authentication via DocuSign password
With Signing Reasons (on each tab):
I approve this document

Electronic Record and Signature Disclosure:
Accepted: 5/4/2022 6:22:06 AM
ID: ecde5ad8-202d-427e-8391-16f71453bf4d

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/4/2022 5:42:47 AM
Certified Delivered	Security Checked	5/4/2022 6:22:06 AM
Signing Complete	Security Checked	5/4/2022 6:24:32 AM
Completed	Security Checked	5/4/2022 6:24:32 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, CTI Clinical Trial and Consulting Services (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Electronic Signature Responsiblities

You agree that your electronic signature is the equivalent of a hand-written signature and that you are responsible for actions initiated using your electronic signature. You agree to report unauthorized usage to CTI upon discovery of such usage via email to esign@ctifacts.com.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to

receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact CTI Clinical Trial and Consulting Services:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
Please send an email to esign@ctifacts.com

To advise CTI Clinical Trial and Consulting Services of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at esign@ctifacts.com and in the body of such request you must state: your previous email address, your new email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from CTI Clinical Trial and Consulting Services

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to esign@ctifacts.com and in the body of such request you must state your email address, full name, mailing address, and telephone number.

To withdraw your consent with CTI Clinical Trial and Consulting Services

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to esign@ctifacts.com and in the body of such request you must state your email, full name, mailing address, and telephone number.

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify CTI Clinical Trial and Consulting Services as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by CTI Clinical Trial and Consulting Services during the course of your relationship with CTI Clinical Trial and Consulting Services.