Humira® for subcutaneous use only

Special drug-use survey

-Long-term survey on Crohn's disease-

Final report

Statistical Analysis Plan

-Ver. 1.0-

Prepared on Apr 02, 2018

1. Approval

Entruster

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Approved by	Post-marketing Surveillance Supervisor	Seal
Date of approval	MMM, DD, YYYY	
Approved by	Medical Supervisor	Seal
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Approved by	Safety Management Supervisor	Seal
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Date of approval	MMM, DD, YYYY	

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1. Preparation/revision history

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
1.0	APR 02,2018	[redacted]	First version

2. Definitions of terms and abbreviations

The terms and abbreviations used in this analysis plan are as follows:

Term and abbreviation	Definition
Adverse event	Any untoward or unintended symptoms (including abnormal laboratory findings), condition or illness which are not always related to Humira.
Adverse events in the safety analysis period	Adverse events which occur from the first administration date of Humira through Week 160 of administration (Day 1 + 1120). Note that if a date is not provided, it should also be included in the period for analysis.
Adverse events not in the safety analysis period	Adverse events which occur prior to the first administration date of Humira or beyond Week 160 of administration (Day 1 + 1120).
Adverse reaction	Adverse events for which the causal relation with Humira cannot be ruled out.
Adverse reactions in the safety analysis period	Adverse events which occurred in the safety analysis period and for which the causal relation with Humira cannot be ruled out.
Adverse reactions not in the safety analysis period	Adverse events which occurred not in the safety analysis period and for which the causal relation with Humira cannot be ruled out.
MedDRA/J	Medical Dictionary for Regulatory Activities / Japanese edition
SOC	System Organ Class in MedDRA/J
PT	Preferred Terms in MedDRA/J
LLT	Lowest Level Terms in MedDRA/J
CDAI	Crohn's Disease Activity Index
WPAI	Work Productivity and Activity Impairment Questionnaire : Crohn's Disease
CRP	C-reactive protein
GB	Green book. Guide on re-examination

3. Objective of this statistical analysis plan

3.1. Objective of developing this statistical analysis plan

This statistical analysis plan aims at planning in advance the items regarding the statistical analysis activities which are conducted in accordance with the protocol of "Special drug-use survey for Humira® for subcutaneous use only (the long-term survey on Crohn's disease)" (hereinafter referred to as "this survey"). This is a survey conducted in accordance with GPSP Ministerial Ordinance, and is a document used to prepare the regulatory report of Humira's special drug-use survey and application documents for re-examination.

4. The survey outline

4.1. Survey objective

The survey aims to collect information on the safety (especially, the onset status of malignant tumour and serious infections) and the effectiveness in Crohn's-disease patients who used Humira® for subcutaneous use only (hereinafter, this drug) and to review and discuss the safety and effectiveness.

<Priority survey items>

Onset status of malignant tumour, serious infection, etc.

4.2. Survey plan

The target patients for this survey should satisfy the following items when the survey is started:

[1] A Crohn's-disease patient who is a suitable candidate for the indication, dosage and administration of Humira

[2] A patient with no malignant tumour in medical history and as complication.

[3] A patient who is not treated with this drug today

4.3. Target sample size for the survey

500 patients

The incidence of malignant tumour when this drug was approved was 1.1% (1/90) in the domestic clinical study and 1.1% (16/1459) in the overseas clinical study in Crohn's disease-patients, showing that malignant tumour occurred in approximately 1.0% of the patients both in Japan and overseas. Therefore, we have a sample size of approximately 300 patients for this survey to detect at least one patient who develops malignant tumour with a power of 95%. We are going to register 500 patients in view of possible withdrawals and dropouts in the follow-up period.

5. Items to be analyzed and the methods

5.1. Items for analysis

1) Items regarding patient composition

[1] The number of registered patients

[2] The number of patients whose survey form was collected

[3] The number of patients in the safety analysis group

[4] The number of patients in the effectiveness analysis group

2) Items regarding safety

[1] A list of the onset status of adverse reactions/malignant tumour/infections

[2] Possible factors which may affect the safety

・Incidence of adverse reactions per patient background, etc.

[3] The onset status of adverse events

・A list of the onset status of serious adverse events

[4] The administration-error status at self-administration

3) Items regarding effectiveness

CDAI, WPAI:CD, Endoscopy, CRP

4) Others

We are going to stratify and analyze malignant tumour, tuberculosis, serious infections, etc.

5.2. Analysis method

Appropriate tests including χ^2 test are employed for analysis, depending on the analysis-data scale and the characteristics.

6. Presence/absence of analysis and its schedule

Analysis objective	The survey's reporting interval and the deadline of re-examination
Final report	From November, 2011 to March, 2017

7. Softwares/dictionary used for analysis

7.1. Statistical analysis and listing softwares

The softwares and their versions for use are as follows:

	Software and version
OS	We use Microsoft Windows 7 or a more recent version.
Statistical analysis software	We use SAS Ver. 9.2 or a more recent version.
Listing software	We use Microsoft Excel 2010 or a more recent version.

7.2. Dictionary for use

The dictionaries used for the names of adverse events, complications, and drugs are as follows:

Item	Dictionary and its version	Remarks
Types of adverse events and adverse reactions/infections	Medical Dictionary for Regulatory Activities / Japanese edition (MedDRA/J 20.1)	・ They are classified into a System Organ Class (SOC) and the appropriate term among the preferred terms (PT) is selected for description. ・ SOC is displayed in accordance with the international agreement. ・ The MedDRA/J version used will be provided in a blank space.
Drug name (concomitant medication)	Iyakuhinmei Data File (IDF) *An appropriate version is applied, depending on the analysis period.	・ A 7-digit code is used, in principle, when concomitant medications are counted per product. ・ Give a priority to the lowest level codes when using codes for the list of concomitant medications (including Re-examination Attachment Form 3).

8. The definition of the groups used for analysis

Name of group	Definition
Patients for registration	Patients whose registration was fixed.
Patients whose survey form was locked	The patients for whom the survey form was locked.
Patients whose survey form was yet to be locked	Patients whose survey form was yet to be locked
Patients excluded from the safety analysis group	The patients whose survey form has been locked and who satisfy the criteria of the patients excluded from the safety analysis group. See "Document for Inclusion/exclusion of patients (for final reporting)" for the criteria to exclude patients from the safety analysis group.
Patients in the safety analysis group	The remaining patients after the patients excluded from the safety analysis group are removed from the patients whose survey form was locked.
Patients excluded from the effectiveness analysis group	Patients who satisfy the exclusion criteria of the effectiveness analysis. See "Document for Inclusion/exclusion of patients (for final reporting)" for the criteria to exclude patients from the effectiveness analysis group.
Patients in the effectiveness analysis group	The remaining patients after those excluded from the effectiveness analysis group are removed from the patients in the safety analysis group.

9. General agreement items for analysis

9.1. Handling of missing data

The relevant item's definition at Chapter 10 or thereafter defines how to impute data. In addition, for date imputation, follow the table below to impute the dates.

Item	Entry data			Dates after imputation	Replacement
	year	month	day		
Chest X ray, Thoracic CT, other imaging, Tuberculin test, QuantiFeron test, endoscopy	2018	1	null	January 1, 2018	If a date is null, regard it as the first day of the month.
	2018	1	-97	January 1, 2018	If a date is unknown, regard it as the first day of the month.
	2018	1	The first 10 days of a month	January 1, 2018	If a date is any of the first 10 days of a month, regard it as the first day of the month.
CRP	2018	1	null	null	If the date is null, it is regarded as null.
	2018	1	The end of a month	January 31, 2018	If the date is "the end of month", replace it with the actual end date of the applicable month.
CDAI	null	1	1	null	If a year is null, it is regarded as null.
General (including the items above and WPAI)	-97	-97	-97	null	If a year, a month and a date are all unknown, they are regarded as null.
	null	null	null	null	If a year, a month and a date are all null, they are regarded as null.
	2018	-97	-97	null	If a month and a date are unknown, they are regarded as null.
	2018	null	null	null	If a month and a date are null, they are regarded as null.

9.2. Descriptive statistics

The following will be calculated for categorial data and quantitative data.

Data type	Item to be calculated
Categorical data	Number of patients, percentage, etc. When the percentage is calculated, the number of patients of "unknown/not provided" is included in the denominator. Chapter 13 stipulates the details regarding the setting of denominators. The patients of "unknown" and "not provided" are excluded in the statistical test.
Quantitative data	Summary statistics: number of cases, mean, standard deviation, median, minimal value, maximal value, 1st quartile value, and 3rd quartile value

9.3. Display digit for figures

The display digit for figures is as follows:

Type of figure	Display digit
Mean, standard deviation, median, 1st quartile value, 3rd quartile value, 95% confidence interval	The figure in the significant digit + 2 digits of data is rounded off to the figure in the significant digit of data + 1 digit for display.
Minimal value, maximal value	The same number of digits is used for the significant digit of data.
Number of patients	Displayed as a whole number
Percentage	The figure is rounded off to the nearest one decimal place for display. When figures for Attachment Form 2, incidences of adverse events, etc are rounded off to two decimal places, the details are specified in the chart layout.
p value	Round the 5 decimal places down to the 4 decimal places. When the figure is smaller than 0.0001, display it as <0.0001 across the board.
Significant digit	The figure for duration of illness should be displayed with the significant digit rounded to the one decimal place. For others, the display digit of data should be the significant digit. As for CRP, the summary statistics except the number of patients should be rounded off to two decimal places.

9.4. Figure display rule

Case	Display rules
If a figure is incalculable	Hyphen "-"

9.5. Statistical test method

The test does not include the classification of unknown/not provided. In principle, the first layer is subjected to the intersegmental test of classified data. Multiplicity is not adjusted.

9.6. Significant level

In principle, the significant level is 5%, two-tailed. $p<0.05$ (<5%) shall be considered significant.

10. Derivation and calculation methods for data

10.1. General

Data name	Derivation and calculation methods
Number of sites for this survey	Aggregate the number with DCF code.
The first administration date of Humira	It shall be the oldest date among the dates described in "the administration status of Humira" in the survey form.
The final administration date of Humira	Do not use for analysis the record of the first administration date of Humira + 1092 days < the first administration date among the data described in "the administration status of Humira" in the survey form. The final administration date of Humira shall be the most recent date among the final administration dates imputed in the following [1] to [4]: [1] Sort data in the order of "the first administration date" of "the administration status of Humira", dosing frequency and description. [2] If the final date is provided, there is no check on the checkbox of "continued", and the final administration date can be identified, select the date described as the final administration date. If the final date is not described, the checkbox of "continued" is checked, and the final administration date cannot be identified, follow the below: ● The final record: Impute the first administration date of Humira + 1092 days on the final administration date. ● Other than the final record: Impute the first administration date of the next record - 1 day on the final administration date. [3] Even though the final dates are described, but the final administration date is incomplete and cannot be identified, follow the below: ● If the year and month are described but the date is unknown, impute the final date of the month as the final administration date. ● If the year is described and the month and date are unknown, impute the final date of the year as the final administration date. If the next record has already been generated and the first administration date of the next record comes earlier than the imputed date, impute the first administration date of the next

Data name	Derivation and calculation methods
	record - 1 day for the final administration date. Of note, if the final administration date is provided in the record where the final administration date of Humira has been identified according to the above rule and the "continued" checkbox is checked, follow the below: ● If the described final administration date > the final administration date imputed according to the above rule, select the imputed final administration date as the final administration date of Humira for the patient. ● If the described final administration date <= the final administration date imputed according to the above rule, select the described final administration date as the final administration date of Humira for the patient. If the first administration date of Humira + 1092 days < the final administration date of Humira imputed according to the above rule, select the first administration date of Humira + 1092 days as the final administration date of Humira.
Days to the final administration date of Humira	The final administration date of Humira - the first administration date of Humira + 1
Total exposure period (in years)	(Days to the final administration date of Humira + 28) / 364
Discontinued patients	• Patients whose final administration date of Humira comes before the first administration date of Humira + 1064 (Week 152) • Patients with a washout period with 60 days or longer. *The final administration date of Humira should be the administration date right before the washout of ≥60 days starts.
Reason for discontinuation	When a reason for discontinuation is described in the survey form, it is defined as 'with' reason for discontinuation. When no such description is found, it is defined as an "unknown/not provided".
Death cases	At least a piece of data on "death" is found as the outcome of the adverse events during the safety analysis period.
Pediatrics	Patients aged <15 years
The elderly	Patients aged ≥65 years

Data name	Derivation and calculation methods
Presence/absence of complications	When complication data are contained in the survey form, it should be classified as “with complications”. When the description in the survey form is not clear enough (when the check of with/without complications is not assessable or when multiple checkboxes are checked), it should be ‘unknown” while no description should be ‘not provided’. Other cases are “no complications”.
Complication/Hepatic function disorder	When liver-disorder data are contained in “171210 Complications.xlsx”, it should be classified as “with hepatic function disorder”. When the description in the survey form is not clear enough (when the check of with/without complications is not assessable or when multiple checkboxes are checked), it should be ‘unknown” while no description should be ‘not provided’. Other cases are “no hepatic function disorder”.
Complication/Renal impairment	When renal-disorder data are contained in “171210 Complications.xlsx”, it should be classified as “with renal impairment”. When the description in the survey form is not clear enough (when the check of with/without complications is not assessable or when multiple checkboxes are checked), it should be ‘unknown” while no description should be ‘not provided’. Other cases are “no renal impairment”.
Complication/Blood disorder	When blood-disorder data are contained in “171210 Complications.xlsx”, it should be classified as “with blood disorder”. When the description in the survey form is not clear enough (when the check of with/without complications is not assessable or when multiple checkboxes are checked), it should be ‘unknown” while no description should be ‘not provided’. Other cases are “no blood disorder”.
Complication/Respiratory disorder	When respiratory-disorder data are contained in “171210 Complications.xlsx”, it should be classified as “with respiratory disorder”. When the description in the survey form is not clear enough (when the check of with/without complications is not assessable or when multiple checkboxes are checked), it should be ‘unknown” while no description should be ‘not provided’. Other cases are “no respiratory disorder”.
Complication/others	When other data are contained in “171210 Complications.xlsx”, it should be classified as “with others”. When the description in the survey form is not clear enough (when the check of with/without complications is not assessable or when multiple checkboxes are checked), it should be ‘unknown” while no description should be ‘not provided’. Other cases

Data name	Derivation and calculation methods
	are “no others”.
Intestinal complications	Classify the complications as mentioned in the presence/absence of intestinal-complications column of survey form. Of note, if the presence/absence check is not assessable or multiple checkboxes are checked, it should be classified into ‘unknown’, while no description should be ‘not provided’.
Non-intestinal complications	Classify the complications as mentioned in the presence/absence of non intestinal-complications column of survey form. Of note, if the presence/absence check is not assessable or multiple checkboxes are checked, it should be classified into ‘unknown’, while no description should be ‘not provided’.
Presence/absence of medical history	When medical-history data are contained in the survey form, it should be classified as “with medical history”. When the checkbox of ‘medical history unknown’ is checked, it should be ‘unknown’ while no description should be ‘not provided’. Others are “no medical history”.
Medical history: tuberculosis	When medical-history data on tuberculosis are contained in “180111 medical history.xlsx”, it should be classified as “with medical history of tuberculosis”. When the checkbox of ‘medical history unknown’ is checked, it should be ‘unknown’ while no description should be ‘not provided’. Others are “no medical history of tuberculosis”.
Medical history: non-tuberculous mycobacteriosis	When medical-history data on non-tuberculous mycobacteriosis are contained in “180111 medical history.xlsx”, it should be classified as “with medical history of non-tuberculous mycobacteriosis”. When the checkbox of ‘medical history unknown’ is checked, it should be ‘unknown’ while no description should be ‘not provided’. Others are “no medical history of non-tuberculous mycobacteriosis”.
Medical history: interstitial pneumonia	When medical-history data on interstitial pneumonia are contained in “180111 medical history.xlsx”, it should be classified as “with medical history of interstitial pneumonia”. When the checkbox of ‘medical history unknown’ is checked, it should be ‘unknown’ while no description should be ‘not provided’. Others are “no medical history of interstitial pneumonia”.
Medical history: bronchitis bacterial	When medical-history data on bronchitis bacterial are contained in “180111 medical history.xlsx”, it should be classified as “with medical history of bronchitis bacterial”. When the checkbox of ‘medical history unknown’ is checked, it should be ‘unknown’ while no description

Data name	Derivation and calculation methods
	should be 'not provided'. Others are "no medical history of bronchitis bacterial".
Medical history: aplastic anaemia	When medical-history data on aplastic anaemia are contained in "180111 medical history.xlsx", it should be classified as "with medical history of aplastic anaemia". When the checkbox of 'medical history unknown' is checked, it should be 'unknown' while no description should be 'not provided'. Others are "no medical history of aplastic anaemia".
Medical history: pancytopenia	When medical-history data on pancytopenia are contained in "180111 medical history.xlsx", it should be classified as "with medical history of pancytopenia". When the checkbox of 'medical history unknown' is checked, it should be 'unknown' while no description should be 'not provided'. Others are "no medical history of pancytopenia".
Medical history: malignant tumour	When medical-history data on malignant tumour are contained in "180111 medical history.xlsx", it should be classified as "with medical history of malignant tumour". When the checkbox of 'medical history unknown' is checked, it should be 'unknown' while no description should be 'not provided'. Others are "no medical history of malignant tumour".
Patients with an hepatitis B virus infection	"Hepatitis" "Hepatitis virus carrier" in "Complications" and/or "Medical history" of "1. Patient information" in the survey form → hepatitis viral infections. If "B" in "Complications" and/or "Medical history" is selected, classified the patients as those with hepatitis B virus infection. In addition, a patient with any events of MedDRA PT code provided in "Patients with hepatitis 180111B virus infection.xlsx" should be also classified as a patient with hepatitis B virus infection.
Presence/absence of administration of anti-hepatitis B virus agent	If the following drug codes are included in the survey form, regard the case as "with administration of an anti-hepatitis B virus agent". Others are "without administration of an anti-hepatitis B virus agent". Entecavir (Baraclude): 6250029 Tenofovir (Tenozet, Viread): 6250024 Adefovir (Hepsera): 6250026 Lamivudine: 6250006, 6250020
Presence/absence of allergy history	When allergy data are contained in the survey form, it should be classified as "with allergy history". When the checkbox of 'medical history unknown' is checked, it should be 'unknown' while no

Data name	Derivation and calculation methods
	description should be 'not provided'. Others are "no allergy history".
Presence/absence of smoking history	When the checkbox of 'with' smoking history is checked in the survey form, regard it as 'with' smoking history. When the checkbox of 'no' smoking history is checked in the survey form, regard it as 'without' smoking history. When the checkbox of 'unknown' for smoking history is checked in the survey form, regard it as 'unknown'. If nothing is described in the survey form, it should be 'not provided'.
Details of smoking history	For the items for smoking history in the survey form, when the 'smoking' checkbox is checked or when the smoking years column is checked of the 'smoking' checkbox, regard it as "smoking". When smoking "in the past" is checked other than "smoking" or when the smoking years for "in the past" is provided, regard it as "only in the past". When a case is not applicable to "smoking" or "only in the past" though a smoking history exists, regard it as "unknown".
Administration status	[1] 1st administration: as a patient with a dose of 160mg [2] 2nd administration: 2nd administration date - the first administration date = 14 days ±4 days or less, and a patient with a dose of 80mg. [3] 3rd administration: 3rd administration date - the 2nd administration date = 14 days ±4 days or less, and a patient with a dose of 40mg. [4] 4th administration and thereafter: the dosing frequency "once every 2 weeks" is checked in the survey form, and a patient with a dose of 40mg * If the patient receives the fourth administration and thereafter, all the administration status should be the condition as shown in [4]. If all the following [1] to [4] are satisfied, aggregate the data as "160mg→80mg→40mg once every two weeks". Others are aggregated as "others". Of note, when data on administration status include only [1], [2] and [3] or when the data ends halfway for some reason, determine whether the case satisfies the criteria from [1] to [4] as of the final data on administration status, and classify it.

Data name	Derivation and calculation methods
Administration status (total number of dosing, total dose)	• Dosing frequency [1] Sort data in the order of "the first administration date" of "the administration status of Humira", dosing frequency and description. [2] Calculate the dosing interval per data on administration status. "When "once every two weeks" is checked, regard it as a 14-day interval. For others, obtain the frequency from "dosing interval". [3] Calculate the dosing frequency per data on administration status. Dosing frequency = (the final administration date (the date imputed based on the definition of 10.1 Final administration date of Humira) – the first administration date(after imputed))/dosing frequency (number of days) When the results of [4] and [3] are ">0" (bigger than 0) and "<1" (smaller than 1), count it as 1. If the figure is ">=1" (1 or bigger), round the decimal down to the integer for the dosing frequency. [5] The total number of dosing shall be the total of [4] per patient. • Dose [1] When the dose of Humira is 'others', obtain the dose from "Dose_other description". [2] Calculate the dose per data of the administration status. Dose = the number of dosing * a dose [3] The total dose should be the total of [2] per patient. • The mean of a dose The mean of a dose = the total dose/the total number of dosing
Patients with self-administration	The patients whose registration form has a check on self-administration.
Age	It should be identified based on the date of birth or the first administration date of Humira in the survey form. Of note, if the "date" of birth is incomplete and not provided, impute 1 as the date. When the date of birth is still incomplete even after the above imputation, just mirror the age provided in the survey form.
Indication	If multiple checkboxes such as Crohn's disease or others are selected for indication in "1. Patient information" in the survey form, count the number for each indication. Note that Crohn's disease should be selected

Data name	Derivation and calculation methods
	to display the item of indication in Attachment Form 3.
Tuberculin test	Conducted :When the first administration date of Humira is 1 and a day before the first administration date is -1, the patients who underwent Tuberculin test between -90 and 1 are regarded as the patients with Tuberculin test. Of note, the data in the survey form shall be used. Not conducted: other than the above
QuantiFeron test	Conducted: When the first administration date of Humira is 1 and a day before the first administration date is -1, the patients who underwent QuantiFeron test between -90 and 1 are regarded as the patients with QuantiFeron test. Of note, the data in the survey form shall be used. Not conducted: other than the above
Chest X ray test	Conducted: When the first administration date of Humira is 1 and a day before the first administration date is -1, the patients who underwent Chest X ray test between -90 and 1 are regarded as the patients with Chest X ray test. Of note, the data in the survey form shall be used.
Thoracic CT test	Conducted: When the first administration date of Humira is 1 and a day before the first administration date is -1, the patients who underwent thoracic CT scan between -90 and 1 are regarded as the patients with thoracic CT scan. Of note, the data in the survey form shall be used.
Imaging procedure	Conducted: When the first administration date of Humira is 1 and a day before the first administration date is -1, the patients who underwent chest X ray, thoracic CT scan, or other imaging tests between -90 and 1 are regarded as the patients with imaging test. Of note, the data in the survey form shall be used.
Tuberculosis test	The patients who underwent (Tuberculin test or QuantiFeron test) and (chest X ray, thoracic CT scan, or other imaging tests). Of note, the data in the survey form shall be used.
Patients subject to AAA measurement	Patients who are included in “CD Long AAA Measurement (final report).xlsx”.
Patients of contraindications	The patients whose registration form has at least a check on the checkbox of contraindications.
Patients who developed an infection	The patients with an infection in an external file “The priority survey item list_ MedDRA20.1_FIX.xlsx”.
Patients who developed malignant tumour	The patients with malignant tumour in an external file “The priority survey item list_ MedDRA20.1_FIX.xlsx”.
Duration of illness (in	“For XX years and XX months” should be converted into the figure in

Data name	Derivation and calculation methods
years)	years for “duration of illness” of “patient information” in the survey form. When both figures of year and month: year + month/12 When the figure of year is provided: year When the figure of month is provided: month/12 Other cases are identified as “unknown/not provided” as the duration cannot be identified.
Concomitant medication	Concomitant medications should the data satisfying the following rules: When concomitant-medication data are contained in the survey form, it should be classified as “with concomitant medications”. When “presence/absence of anti-tuberculosis drug”, “presence/absence of concomitant medications” in the survey form are not assessable, select “unknown” while they are not provided, select “not provided”. Other cases are “without concomitant medications”. ◆Data with a drug name in “administration status of anti-tuberculosis drug”, “concomitant medications” of the survey form ・ When ‘from before Humira administration is started” is checked, the first administration date should be the same as the first administration date of Humira”. ・ When the year and month are described for the first administration date of the concomitant medication, impute “1” for the “date”. ・ When the year is described for the first administration date of the concomitant medication, impute “1” each for the “month” and “date”. ・ When ‘continued’ is checked, the final administration date should be the same as the final administration date of Humira. ・ When the year and month are described for the final administration date of the concomitant medication, impute the month’s final date for the date. ・ When the year is described for the final administration date of the concomitant medication, impute “12” for the month and “31” for the date. ・ When the final administration of concomitant medication < the first administration date of Humira, and/or when the final administration date of Humira < the first administration date of concomitant

Data name	Derivation and calculation methods
	medication, exclude the case from the calculation for concomitant medication. If the above imputing methods do not help add the date (the first administration date or the final administration date is not provided, etc.), or if the first administration date and the final administration date of concomitant medication are reversed, it should be regarded as a concomitant medication. ('Clear' refers to a condition where no ambiguous expressions like "around", "in the middle", etc. are included and a number or figure only is provided.)
Concomitant medication: aminosalicylic acid products	See the drug code list and determine from the drug codes.
Concomitant medication: corticosteroid	See the drug code list and determine from the drug codes.
Concomitant medication: immunosuppressant	See the drug code list and determine from the drug codes.
Concomitant medication: antibiotics	See the drug code list and determine from the drug codes.
Concomitant medication: others	Others are the drugs other than aminosalicylic acid products, corticosteroid, immunosuppressant, and antibiotics.
Prior medication: TNFα drug	When presence/absence treatment history with anti-TNFα drug is "present" in "treatment history with anti-TNFα drug for Crohn's disease" of the survey form, it should be classified as "with" the history. When the assessment is impossible based on the checkbox, it should be classified as "unknown" whereas no description should be "not provided". Other cases are "without" the history.
Prior medications	When a patient had a prior medication of TNFα drug and any of the prior-medication type checkboxes is checked, the patient is regarded as "with prior medications". When the assessment is impossible based on the checkbox of presence/absence of prior medication/treatment, regard it as "unknown" while no description should be "not provided". Other cases are "without" prior medications.

Data name	Derivation and calculation methods
Prior medication: aminosalicylic acid products	If aminosalicylic acid drug in the survey form is checked, regard the case as “with aminosalicylic acid drug”. Others are “without aminosalicylic acid drug”.
Prior medication: corticosteroid	If corticosteroids in the survey form is checked, regard the case as “with corticosteroids”. Others are “without corticosteroids”.
Prior medication: immunosuppressant	If immunosuppressant in the survey form is checked, regard the case as “with immunosuppressant”. Others are “without immunosuppressant”.
Prior medication: antibiotics	Otherwise, when antibiotics in the survey form is checked, regard the case as “with antibiotics”. Others are “without antibiotics”.
Prior treatment	When any of the checkboxes of each prior-treatment type in “prior medication/treatment for Crohn's disease is checked in the survey form, regard it as “with prior treatment”. When the assessment is impossible based on the checkbox of presence/absence of prior medication/therapy, regard it as “unknown” while no description should be “not provided”. Other cases are “without” prior treatment.
Prior treatment: surgery	Refer to “[Humira CD Long] Conversion data provided for analysis” to identify it.
Prior treatment: granulocyte and monocyte adsorption apheresis (GCAP)	When GCAP is checked in the survey form, regard it as “with GCAP”. Others are “without GCAP”.
Prior treatment: enteral nutrition therapy	When enteral nutrition therapy is checked in the survey form, regard it as “with enteral nutrition therapy”. Others are “without enteral nutrition therapy”.
Prior treatment: intravenous nutrition therapy	When intravenous nutrition therapy is checked in the survey form, regard it as “with intravenous nutrition therapy”. Others are “without intravenous nutrition therapy”.
Concomitant therapy	It should be described in “non-medicinal treatment/concomitant therapy for Crohn's disease” of the survey form. The data from the first administration date to the final administration date of Humira will be calculated. When concomitant-therapy data are contained under the same rule as the definition of concomitant medications defined in “10.1 General”, regard it “with concomitant therapy”. When “presence/absence of concomitant therapy” in the survey form is not assessable, select “unknown” while it is not provided, select “not provided”. Other cases are “without

Data name	Derivation and calculation methods
	concomitant therapy".
Concomitant therapy: surgery	Refer to "[Humira CD Long] Conversion data provided for analysis" to identify it.
Concomitant therapy: GCAP	When GCAP is checked in the survey form, regard it as "with GCAP". Others are "without GCAP".
Concomitant therapy: enteral nutrition therapy	When enteral nutrition therapy is checked in the survey form, regard it as "with enteral nutrition therapy". Others are "without enteral nutrition therapy".
Concomitant therapy: intravenous nutrition therapy	When intravenous nutrition therapy is checked in the survey form, regard it as "with intravenous nutrition therapy". Others are "without intravenous nutrition therapy".
Work condition	Just mirror the checked information at "work condition" in the survey form. Of note, if multiple checkboxes are checked or the check is not assessable, regard it as "unknown". When none of the items are checked, it should be "not provided".

10.2. Safety analysis

Data name	Derivation and calculation methods
Adverse event	The adverse events for analysis should include not only the events derived from the survey form but also the events covered in the detailed investigation which has been described by the physicians at a contracted site/department even though not derived from the survey form in "Humira CD Long_AE matching list". With adverse event: at least 1 record on adverse event(s) exists Without adverse event: other than the above. When adverse events are counted per SOC, the identical SOC in a patient should be counted as 1 whereas the same PT in the same patient be counted as 1 for PT. When no applicable patients were observed, display "0" for the number of patients and "0.00" for the percentage.
Seriousness of adverse events	Based on the seriousness criteria for company assessment which are provided in "Humira CD Long_AE matching list", regard the events which have been assessed to be serious as serious adverse events. With serious adverse event: at least 1 record on serious adverse event(s) exists Without serious adverse event: other than the above. Follow the way of counting adverse events to count serious adverse

Data name	Derivation and calculation methods
	events. Give the following priority to serious adverse events for aggregation. [1]serious [2]non-serious
Causal relationship of adverse events	Unless a serious adverse event is assessed as "not related" in the company causality assessment provided in "Humira CD Long_AE matching list", regard the event as 'with' causal relationship. Give the following priority to causal relationship for aggregation. [1] With causal relationship [2] without causal relationship
Outcome of adverse events	Use the outcomes for company assessment provided in "Humira CD Long_AE matching list" to give the following priority to the outcomes for aggregation based on the rules in "derivation and calculation methods" for adverse events. [1] [1] death [2] unknown [3] not recovered [4] recovered with sequela [5] recovering [6] recovered [7] not provided
Days from the first administration date of Humira to the adverse-event onset date	Use the onset date for company assessment provided in "Humira CD long-term_AE matching list". When the first administration date of Humira and the adverse-event onset date can be identified as the complete date, they can be used for calculation. When the first administration date of Humira <= the adverse-event onset date: Adverse-event onset date - the first administration date of Humira + 1 When the first administration date of Humira > the adverse-event onset date: Adverse-event onset date - the first administration date of Humira When more than one identical PT is found in a patient, use the first onset date to identify the adverse event to be counted.
Days from the adverse-event onset date to the outcome confirmation date (recovered or recovering)	Use the onset date and the outcomes (recovered or recovering) for company assessment provided in "Humira CD Long_AE matching list". When the adverse-event onset date and the outcome confirmation date can be identified as the complete date, they can be used for calculation. Outcome confirmation date - adverse-event onset date + 1 When more than one identical PT is found in a patient, choose the event which persisted longest until the recovery or the outcome confirmation date.

Data name	Derivation and calculation methods
Incidence of adverse reactions, incidence of serious adverse reactions, incidence of adverse events, incidence of serious adverse events	Calculate the incidence of adverse reactions, incidence of serious adverse reactions, incidence of adverse events, incidence of serious adverse events with the number of patients with any of the reactions/events in numerator and the number of patients in the safety analysis group in denominator. Provide how to calculate in each table at Chapter 13 and thereafter if other calculation methods are used.

10.3. Effectiveness analysis

<table>
<tr><th>Data name</th><th>Derivation and calculation methods</th></tr>
<tr><td>Remission</td><td>When the CDAI score is <150, the case is regarded as remission.</td></tr>
<tr><td>WPAI</td><td>
<table>
<tr><td>Q1</td><td>Do you work now?</td><td>Yes, no</td></tr>
<tr><td>Q2</td><td>How many hours did you leave the work due to problems related to Crohn's disease over the past 7 days?</td><td>( ) hour(s)</td></tr>
<tr><td>Q3</td><td>How many hours did you leave the work for a reason other than Crohn's disease such as holidays or hours for which you were off to participate in this survey over the past 7 days?</td><td>( ) hour(s)</td></tr>
<tr><td>Q4</td><td>How many hours did you actually work for the past 7 days?</td><td>( ) hour(s)</td></tr>
<tr><td>Q5</td><td>How much productivity was affected by Crohn's disease while you were working over the past 7 days?

0: Crohn’s disease did not affect the work.
10: Crohn's disease completely interrupted the work.
Based on the above, your score between 0 to 10.</td><td>( )</td></tr>
<tr><td>Q6</td><td>How much did Crohn's disease affect various daily activities except your job over the past 7 days?</td><td>( )</td></tr>
</table>
</td></tr>
</table>

Data name	Derivation and calculation methods
	0: Crohn's disease did not affect daily activities. 10: Crohn's disease completely interrupted daily activities. Based on the above, your score between 0 to 10.
	• Absenteeism (%) Calculate it with the following formula based on the questions (Q1 to Q6) on the above table: [Q2 / (Q2 + Q4)] × 100 • Presenteeism (%) Calculate it with the following formula based on the questions (Q1 to Q6) on the above table: (Q5 / 10) × 100 • Overall work impairment (%) Calculate it with the following formula based on the questions (Q1 to Q6) on the above table: { Q2 / (Q2 + Q4) + [1 - Q2 / (Q2 + Q4)] × (Q5 / 10) } × 100 • Activity Impairment (%) Calculate it with the following formula based on the questions (Q1 to Q6) on the above table: (Q6 / 10) × 100

11. How to stratify data

Data	How to stratify
Dosage and administration	160mg→80mg→40mg once every two weeks, other
Dosing frequency (times)	≥1 and <4, ≥4 and <13, ≥13 and <26, ≥26 and <39, ≥39 and <52, ≥52 and <65, ≥65 and <78, ≥78
Total dose (mg)	<500mg, ≥500mg and <1000mg ≥1000mg and <2000mg ≥2000mg and <3000mg ≥3000mg, Unknown
Dose period	the first administration to Week 4 of administration, after Week 4 of administration to Month 3 of administration, after Month 3 of administration to Month 6 of administration, after Month 6 of administration to Year 1 of administration, after Year 1 of administration to Year 1 and Month 6 of administration, after Year 1 and Month 6 of administration to Year 2 of administration, after Year 2 of administration to Year 2 and Month 6 of administration, after Year 2 and Month 6 of administration to Year 3 of administration, Continued as of Year 3 of administration
Reason for discontinuation	Development of adverse event, lack of effectiveness, patient's wish, no visit, others
Sex	Man, women, unknown/not provided
Pregnancy/nursing	Not pregnant/nursing, pregnant, nursing, unknown/not provided
Age (in years)	<15, ≥15 and <65, ≥65, unknown/not provided
Body weight (kg)	<30, ≥30 and <40, ≥40 and <50, ≥50 and <60, ≥60, unknown/not provided
BMI(kg/m^2)	<18.5, ≥18.5 and <25, ≥25 and <30, ≥30, unknown
Duration of illness (in	<2, ≥2 and <5, ≥5 and <10, ≥10, unknown/not provided

Data	How to stratify
years)	
Indication	Crohn's disease, other, unknown/not provided
Allergy history	Without the history, with the history, unknown/not provided
Smoking history	Without the history, with the history, unknown/not provided
Details of smoking history	Smoking, only in the past (not smoking now), unknown
HBs antigen	Not conducted, conducted, unknown/not provided
Tuberculosis-test status	Not conducted, conducted
Complications	Without the history, with the history, unknown/not provided
Detailed classification of complications	Liver disorder, renal disorder, blood disorder, respiratory disorder, others
Other classification of complications	Diabetes mellitus, osteoporosis, malignant tumour, others
Medical history	Without the history, with the history, unknown/not provided
Detailed classification of medical history	Tuberculosis, non-tuberculous mycobacteriosis, interstitial pneumonia, bronchitis bacterial, aplastic anaemia, pancytopenia, malignant tumour, others
Prior medications for Crohn's disease	Without the history, with the history, unknown/not provided
Detailed classification of prior medications for Crohn's disease	Anti-TNFα drug, aminosalicylic acid products, corticosteroid, immunosuppressant, and antibiotics.
Prior treatment for Crohn's disease	Without the history, with the history, unknown/not provided
Detailed classification of prior treatment for Crohn's disease	Surgery, GCAP, enteral nutrition therapy, intravenous nutrition therapy, others
Treatment history with anti-TNFα drug	Without the history, with the history, unknown/not provided
Reason for discontinuation of treatment history with anti-TNFα drug	Lack of efficacy, adverse events, others, unknown/not provided
Concomitant medication	Without the history, with the history, unknown/not provided
Detailed classification	Aminosalicylic acid products, corticosteroid, immunosuppressant,

Data	How to stratify
of concomitant medications	antibiotics, and others
Concomitant therapy for Crohn's disease	Without the history, with the history, unknown/not provided
Detailed classification of concomitant therapy for Crohn's disease	Surgery, GCAP, enteral nutrition therapy, intravenous nutrition therapy, others
Condition/site of disease in the medical history of Crohn's disease	Anus/perianal region, rectum, stomach/duodenum, colon, jejunum/ileum, other, unknown/not provided
Intestinal complications as condition/site of disease in the medical history of Crohn's disease	Without the history, with the history, unknown/not provided
Non-intestinal complications as condition/site of disease in the medical history of Crohn's disease	Without the history, with the history, unknown/not provided
Work condition	Routinely engaged in wage labor for 35 hours or longer a week, Routinely engaged in wage labor for 35 hours or less a week, Not engaged in wage labor but do housework, shopping, childrearing, exercise, or study , Involved in daily living activities, Involved in less daily activities due to hospitalization, etc. Unknown/not provided
CDAI at the first administration	<150: remission ≥150 and <220: mild ≥220 and <450: moderate >450: severe Unknown/not provided
CRP	<1.0mg/dL, ≥1.0mg/dL,

Data	How to stratify
	Unknown/not provided
Self administration	Without the history, with the history, unknown/not provided

12. Data handling at test/assessment periods

12.1. Assessment period for CDAI, WPAI, CRP and non-intestinal conditions

Time allowance of assessment period with the first administration date of Humira as 1 is as follows:

Assessment period	Time Allowance(Day)
At the first administration	- 1 (scheduled date 1)
Week 4 of administration	15 - 43 (scheduled date 29)
Month 3 of administration	71 - 99 (scheduled date 85)
Month 6 of administration	169 - 197 (scheduled date 183)
Year 1 of administration	337 - 393 (scheduled date 365)
Year 1 and Month 6 of administration	519 - 575 (scheduled date 547)
Year 2 of administration	701 - 757 (scheduled date 729)
Year 2 and Month 6 of administration	883 - 939 (scheduled date 911)
Year 3 of administration	1065 - 1121 (scheduled date 1093)
At final assessment	Final assessment of each patient no matter whether the each assessment period is within Time Allowance.

The data for analysis should derive from the date closest to the scheduled date within Time Allowance. If there are more than one data dated on the same day, select the worst value.

12.2. Assessment period of endoscopy results

Time allowance of assessment period with the first administration date of Humira as 1 is as follows:

Assessment period	Time Allowance(Day)
At the first administration	- 1 (scheduled date 1)
Month 6 of administration	2 - 182 (scheduled date 183)
Year 1 of administration	183 - 364 (scheduled date 365)
Year 2 of administration	365 - 728 (scheduled date 729)
Year 3 of administration	729 - 1092 (scheduled date 1093)
At final assessment	Final assessment of each patient no matter whether the each assessment period is within Time Allowance.

The data for analysis should derive from the date closest to the scheduled date within Time Allowance. If there are more than one data dated on the same day, select the worst value.

12.3. Assessment period for the administration status of Humira

Time allowance of assessment period with the first administration date of Humira as 1 is as follows:

Assessment period	Time Allowance(Day)
the first administration to Week 4 of administration	1-28
after Week 4 of administration to Month 3 of administration	29-84
after Month 3 of administration to Month 6 of administration	85-182
after Month 6 of administration to Year 1 of administration	183-364
after Year 1 of administration to Year 1 and Month 6 of administration	365-546
after Year 1 and Month 6 of administration to Year 2 of administration	547-728
after Year 2 of administration to Year 2 and Month 6 of administration	729-910
after Year 2 and Month 6 of administration to Year 3 of administration	911-1092
Continued as of Year 3 of administration	1093-, patients with 'continued' checked

12.4. Assessment period for the onset status of adverse reactions

Time allowance of assessment period with the first administration date of Humira as 1 is as follows:

Assessment period	Time Allowance(Day)
the first administration to Week 4 of administration	1-28
after Week 4 of administration to Month 3 of administration	29-84
after Month 3 of administration to Month 6 of administration	85-182
after Month 6 of administration to Year 1 of administration	183-364
after Year 1 of administration to Year 1 and Month 6 of administration	365-546
after Year 1 and Month 6 of administration to Year 2 of administration	547-728

Assessment period	Time Allowance(Day)
after Year 2 of administration to Year 2 and Month 6 of administration	729-910
after Year 2 and Month 6 of administration to Year 3 of administration	911-1092
Year 3 of administration -	1093 -

12.5. Assessment period for the continued administration of Humira

The assessment period with the first administration date of Humira as 1 is as follows:

Assessment period	Day
At the first administration	1
Week 4 of administration	29
Month 3 of administration	85
Month 6 of administration	183
Year 1 of administration	365
Year 1 and Month 6 of administration	547
Year 2 of administration	729
Year 2 and Month 6 of administration	911
Year 3 of administration	1093

13. Charts to be generated (chart No., chart name)

13.1. General

"1.1.1 Case structure chart"

Patients for analysis: registered patients

Analysis objective: to indicate changes in the number of patients

Analysis items: number of sites with registered patients, number of registered patients, number of sites with patients whose survey form has been locked, number of patients whose survey form was locked, number of patients whose survey form was yet to be locked, the breakdown of the reasons for unlocked survey forms, number of patients in the safety analysis group, number of patients excluded from the safety analysis group, the breakdown of reasons for exclusion from the safety analysis group, number of patients in the effectiveness analysis group, number of patients excluded from the effectiveness analysis group, the breakdown of reasons for exclusion from the effectiveness analysis group

"1.1.2 Case structure chart on patients in the effectiveness analysis group"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to indicate changes in the number of patients
Analysis items: number of patients in the effectiveness analysis group, number of patients in the CRP analysis group, number of patients in the WPAI analysis group, number of patients in the endoscopy (large intestine) analysis group, and number of patients in the endoscopy (small intestine) analysis group

Note: the definitions of patients in each analysis group are as follows:
Patients in the CRP analysis group: the patients in the effectiveness analysis group whose CRP level was measured after they were started on Humira.
Patients in the WPAI analysis group: the patients in the effectiveness analysis group whose WPAI was measured after they were started on Humira.
Patients in the endoscopy (large intestine) analysis group: the patients in the effectiveness analysis group who underwent endoscopy (large intestine) after they were started on Humira.
Patients in the endoscopy (small intestine) analysis group: the patients in the effectiveness analysis group who underwent endoscopy (small intestine) after they were started on Humira.

"1.2 Number of sites surveyed and number of patients surveyed (patients in the safety analysis group)"

Patients for analysis: patients in the safety analysis group
Analysis objective: to show the number of patients per site
Analysis items: number of sites surveyed, number of patients in the safety analysis group, the mean, the maximum, the minimum of the number of patients in the safety analysis group per site

"1.1.3 Progress in survey forms"

Patients for analysis: patients whose survey form was locked
Analysis objective: to show the number of locked cases for each separate volume per patients whose survey form was locked, patients in the safety analysis group, and patients in the effectiveness analysis group.
Analysis items: locked cases in the 1st separate volume, locked cases in the 2nd separate volume, locked cases in the 3rd separate volume, locked cases in the 4th separate volume, locked cases in the 5th separate volume, locked cases in the 6th separate volume

"1.3 A list of the patients excluded from the safety analysis and the patients excluded from the effectiveness analysis (including the reason for exclusion)"

Patients for analysis: patients whose survey form was locked
Analysis objective: to show the list of patients excluded from each analysis group and the reason for exclusion
Analysis item: The reason for exclusion will be displayed for the patients not in the safety or efficacy

analysis.
If more than one reason for exclusion exists in a patient, display them in a comma-delimited manner.

"1.3.1. Excluded patients (aggregation by reason)"

Patients for analysis: registered patients

Analysis objective: to show a list of the reasons for exclusion in each analysis group regarding all the patients in the analysis group.

Analysis items: case number, patients whose survey form was yet to be locked, patients excluded from the safety analysis group, the reasons for exclusion from the safety analysis (breach of contract: unsigned site/department, breach of contract: unsigned physician, breach of contract: an excess of the number of signed patients, untreated with Humira, administration prior to contract, administration after the contract expires, administration start not in the registration period, breach of registration criteria: deviation of the registration period, breach of registration criteria: not the disease surveyed, breach of registration criteria: malignant tumour, breach of registration criteria: during the administration period of Humira, not confirmed by physician, patients not registered, overlapped patients, safety not assessable, data credibility not confirmed, data credibility not confirmed (breakdown)), patients excluded from the effectiveness analysis, reasons for exclusion from the effectiveness analysis (effectiveness not assessable)

If data credibility cannot be identified and more than one (breakdown) exists in a patient, display them in a comma-delimited manner.

"1.4 A list of patients (adverse event + search flag)"

Patients for analysis: patients whose survey form was locked

Analysis objective: to show a list of background information per patient, adverse events and administration status by using analysis data.

Analysis items: case number, sex, age, body weight, duration of illness, adverse event (presence/absence of adverse event, safety

Patients with adverse events not in the analysis period, SOC code, System Organ Class, PT code, name of disease (MedDRA PT), adverse events reported by physician, onset date, days from the first administration to the onset, seriousness, causality, outcome, outcome confirmation date, days to the outcome confirmation), CDAI effectiveness at the final assessment, administration status of Humira (the first administration date, the final administration date, days of administration, the initial dose, the maximum dose) presence/absence of complication, presence/absence of medical history, hepatitis B virus test (HBs antigen), with/without administration of anti-hepatitis B virus agent, tuberculosis test (Tuberculin test, QuantiFeron test, chest X ray test, thoracic CT scan, other imaging, tuberculosis test) search flags (patients in the safety analysis group, patients in the effectiveness analysis group, death cases, pediatrics, the elderly, pregnant, nursing, liver disorder, renal disorder, patients with hepatitis B viral infection, patients with an infection, patients with malignant tumour,

patients with AAA measured, contraindication)

Note: Follow “12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions” for CDAI effectiveness in the final assessment period.
In addition, display “remission” or “no remission”. Display “unknown” for patients excluded from the effectiveness analysis.

”1.4.1 A list of adverse events”

Patients for analysis: patients whose survey form was locked
Analysis objective: to show a list of adverse events per patient by using analysis data.
Analysis items: case number, sex, age, SOC code, System Organ Class, PT code, name of disease (MedDRA PT), adverse events reported by physician, onset date, days from the first administration date to the onset date, seriousness, causality,
outcome, outcome confirmation date, dates to the outcome, complication, patients in the safety analysis group, the reasons for exclusion from the safety analysis (breach of contract: unsigned site/department, breach of contract: unsigned physician, breach of contract: an excess of the number of signed patients, untreated with Humira, administration prior to contract, administration after the contract expires, administration start not in the registration period, breach of registration criteria: deviation of the registration period, breach of registration criteria:
not the disease surveyed, breach of registration criteria: malignant tumour, breach of registration criteria: during the administration period of Humira, not confirmed by physician, patients not registered, overlapped patients, safety not assessable, data credibility not confirmed, data credibility not confirmed (breakdown)), patients in the effectiveness analysis group, patients who developed adverse events not in the safety analysis period, search flag (death case, pediatrics, the elderly, pregnant, nursing, liver disorder, renal disorder, patients with hepatitis B viral infection, patients with an infection, patients with malignant tumour, patients with AAA measured, contraindication)
If data credibility cannot be identified and more than one (breakdown) exists in a patient, display them in a comma-delimited manner.

“1.4.2 A list of death cases”

Patients for analysis: patients whose survey form was locked
Analysis objective: to show a list of adverse events in death cases by using analysis data.
Analysis items: case number, sex, age, SOC code, System Organ Class, PT code, name of disease (MedDRA PT), adverse events reported by physician, onset date, days from the first administration date to the onset date, seriousness, causality,
outcome, outcome confirmation date, days to the outcome, complication, patients in the safety analysis group, patients in the effectiveness analysis group, patients who developed adverse events not in the safety analysis period, search flag (death case, pediatrics, the elderly, pregnant, nursing,

liver disorder, renal disorder, patients with hepatitis B viral infection, patients with an infection, patients with malignant tumour, patients with AAA measured, contraindication)

"1.4.3 A list of patients aged 18 years or younger"

Patients for analysis: patients whose survey form was locked

Analysis objective: to show a list of patients aged 18 years or younger by using analysis data.

Analysis items: case number, sex, age, height, body weight, BMI, duration of illness, adverse event (SOC code, System Organ Class, PT code, name of disease (MedDRA PT), adverse events reported by physician, onset date, days from the first administration date to the onset date, seriousness, causality, outcome, outcome confirmation date, days to the outcome), administration status of Humira (the first administration date, the final administration date), discontinued/not discontinued, reason for discontinuation, complication (presence/absence of complication, PT code, name of disease (MedDRA PT), medical history (presence/absence of medical history, PT code, name of disease (MedDRA PT)), condition/ medical history of Crohn's disease (anus/perianal region, rectum, stomach/duodenum, colon, jejunum/ileum, others, intestinal complication, non-intestinal complication), prior medications (anti-TNFα drug, aminosalicylic acid drug, corticosteroids, immunosuppressant, antibiotics), CDAI level (at the first administration, Week 4 of administration, Month 3 of administration, Month 6 of administration, Year 1 of administration, Year 1 and Month 6 of administration, Year 2 of administration, Year 2 and Month 6 of administration , Year 3 of administration)

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for CDAI level.

"1.5 Administration status of Humira (dosage and administration)"

Patients for analysis: patients in the safety analysis group, patients in the effectiveness analysis group

Analysis objective: to show the administration status of Humira

Analysis items: count the number of patients who receive Humira in the process of "1st time: 160mg→2nd time: 80mg →3rd time: 40mg once every two weeks, and no change thereafter" and the number of "other" patients, and calculate the percentage to the target patients. See 10.1 for how to classify the administration process.

"1.6.1 Administration status of Humira (dosing frequency, dose)

Patients for analysis: patients in the safety analysis group, patients in the effectiveness analysis group

Analysis objective: to show the dosing frequency and the distribution status of the total dose

Analysis items: calculate the number of patients per segment defined in "11 How to stratify data",

summary statistics and the percentage to the number of patients in the analysis groups regarding dosing frequency and the total dose.

"1.6.2 Administration status of Humira (period)"

Patients for analysis: patients in the safety analysis group, patients in the effectiveness analysis group

Analysis objective: to show the distribution status in the administration period.

Analysis item: Calculate the administration dates based on "days to the final administration date of Humira" of "10.1 General" for the administration period. Then, calculate the number of patients per segment which contains the administration dates in each patient and the percentage to the patients in the analysis group in the Time Allowance defined in "12.3 Assessment period for administration status of Humira". In addition, calculate summary statistics for the number of days for administration.

"1.6.3 Continuation rate of Humira"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the continuation rate of Humira using the Kaplan-Meier method.

Analysis items: Calculate At Risk, number of discontinued patients, continuation rate and 95% of continuation rate per assessment period.

Generate the Kaplan-Meier curve with the percentage of the number of discontinued patients to At Risk as the continuation rate.

Note: Follow "12.5 Assessment period for the continuation of Humira administration" for the dates of assessment period.

The days are censored at the first administration date of Humira + 1092 in patients who are still registered at Year 3.

Calculate the analysis items using the Kaplan-Meier method.

At Risk should include the number of patients who are exposed to a discontinuation risk.

"1.7 Administration status of Humira (discontinuation of administration)"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the number of discontinued patients and the breakdown of the reasons for discontinuation.

Analysis items: Calculate the number of patients in the analysis groups, the percentage to the discontinued patients and patients in the analysis groups, patients 'with' reason for discontinuation and unknown/not provided and the percentage to the number of discontinued patients, number of patients per "reason for discontinuation" defined in "11 How to stratify data" and the percentage to the number of discontinued patients.

Note: the reasons for discontinuation may be overlapped in calculation.
In addition, if there are no patients applicable to “multiple choices”, do not display the items of “multiple choices”.

“1.7.1 Administration status of Humira (reason for discontinuation other reasons)
Patients for analysis: patients in the safety analysis group
Analysis objective: to show a list in which the reason for discontinuation is ‘others’.
Analysis item: Calculate the number of patients classified into “others “of “reasons for discontinuation” defined in “11 How to stratify data” by classified item of “reasons for discontinuation, other reason”.

“1.7.2 Administration status of Humira (a list of reasons for discontinuation other reasons)”
Patients for analysis: patients in the safety analysis group
Analysis objective: to show a list in which the reason for discontinuation is ‘others’.
Analysis item: Display other reasons per case number for patients classified into “others“ of “reasons for discontinuation” defined in “11 How to stratify data”.

“1.12 Distribution status of patient backgrounds”
Patients for analysis: patients in the safety analysis group, patients in the effectiveness analysis group, patients whose survey form was locked
Analysis objective: to show the distribution status of patient backgrounds
Analysis item: calculate the number of patients in the analysis groups.
Calculate the number of patients per the following segment defined in “11 How to stratify data” and the percentage to the number of patients in the analysis groups.
Sex, pregnancy/nursing, age (year), body weight (kg), BMI (kg/m^2), duration of illness (year), indication (registration form), allergy history, smoking history, detailed classification of smoking history, tuberculosis test, hepatitis B virus test status (registration form), complication, detailed classification of complications, complication/others, medical history, detailed classification of medical history, prior medication for Crohn's disease, detailed classification of prior medication for Crohn's disease, prior treatment for Crohn's disease, detailed classification of prior treatment for Crohn's disease, treatment history with anti-TNFα drug for Crohn's disease, reason for discontinuation of treatment history of anti-TNFα drug, concomitant medication, detailed classification of concomitant medications, concomitant treatment for Crohn's disease, detailed classification of concomitant treatment for Crohn's disease, condition/medical history of Crohn's disease (site of disease of condition/medical history of Crohn's disease), intestinal complications of condition/medical history of Crohn's disease, non- intestinal complications of condition/medical history of Crohn's disease), work condition, CDAI when the administration was started, CRP
In addition, calculate summary statistics for the following:

age (year), body weight (kg), BMI (kg/m^2), duration of illness (year), CDAI when the administration was started, CRP

Note: for pregnancy/nursing, calculate the percentage to female patients.
Note: For the discontinuation reasons for anti-TNFα drug, calculate the percentage to the patients with treatment history of anti-TNFα drug.

"1.13 Distribution status of self-administration"
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the distribution status regarding presence/absence of self-administration
Analysis item: calculate the number of patients in the analysis groups.

Calculate the number of patients per "self-administration" defined in "11. How to stratify data" and the percentage to the number of patients in the analysis groups.

"1.16 A list of patients with AAA measured
Patients for analysis: patients in the safety analysis group
Analysis objective: to show a list of patients with AAA measured.
Analysis item: display the following items in "patients with AAA measured" defined in "10.1 General".
Case number, administration status of Humira (the first and final administration dates), concomitant medications, serum anti-adalimumab antibody (blood sampling date, positive/negative) adverse events reported by physician, name of disease (MedDRA PT), System Organ Class, onset date, seriousness, causality, outcome confirmation date, outcome, CDAI remission

13.2. Safety

"2.2 A list of the onset status of serious adverse events (Attachment Form 10)"
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of serious adverse events
Analysis item: aggregate the following items per period for adverse events which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of sites surveyed, number of patients surveyed, number of patients with serious adverse events, number of serious adverse events, incidence of adverse events, incidence of serious adverse events and type of adverse reactions, etc. (SOC, PT).

Note: The classification of period should include at approval, cumulative and total.
Put * before the PT of unexpected events from "Precautions".

"2.3 A list of target-patient summary (Attachment Form 3)"

Patients for analysis: patients whose survey form was locked

Analysis objective: to show a list of patients

Analysis item: provide the items for analysis and the definitions below.

(1) Case number

Provide a serial number starting 1 per patient.

(2) Name of site (company code)

Describe it in Japanese, as the official name. Obtain the name of site from "[CD Long-term]DCF code list_Company A.xlsx" and "[CD Long-term]DCF code list_Company E.xlsx".

(3) Main establishing entity/code

Obtain the code from "Ultmarc re-examination classification".

(4) Name of prefecture where the business is located

Fill in the name. Obtain the prefecture's name from "Ultmarc re-examination classification20150731.xlsx".

(5) Patient abbreviation name

Fill in "not applicable" as mentioned in GB.

(6) Sex

Fill in man, women, unknown or not provided as mentioned in GB.

(7) Date of birth (or age)

Unify it in age. Fill in "A + age + "0000"" as mentioned in GB.

(8) Inpatient/outpatient

Fill in inpatient, outpatient, unknown or not provided as mentioned in GB.

(9) Indication

Code, name of disease: Obtain the MedDRA/J LLT code and LLT from the indication of Humira described in the survey form.

(10) Severity prior to administration

Note: Follow Time Allowance of "12.1 Assessment period for CDAI, WPAI, CRP to show CDAI when the administration was started at the following 4 levels:

<150: remission, ≥150 and <220: mild, ≥220 and ≤450: moderate, >450: severe in severity

(11) Complications

Presence/absence: Refer to the "presence/absence of complications" defined in "10.1 General".

Number of described complications: the number of PT codes encoded by MedDRA/J. If more than 1 identical PT code is found in a patient, count the PT as 1. Describe "0" for the case with no complications.

Term: Describe the PT of complication encoded by MedDRA/J. Arrange detailed classification of complication, the name of complication disease name, a serial number of the complication per patient. Leave the column blank for the case with no descriptions.

(12) Route of administration

Describe it as “SC”.

(13) Maximal dose (a dose)

The maximum of a dose Select the largest number in “administration status defined in “10.1 General” per patient.

(14) The mean dose (a dose)

The mean of a dose

It should be the value of “total dose/total dosing times” based on the “administration status (total dosing time, total dose)” defined in “10.1 General”.

(15) Unit

Use “MG”.

(16) daily dosing frequency (the maximum)

Use “1”.

(17) Period for administration

The value of “total dosing time” based on “ administration status (total dosing time, total dose)” defined in “10.1 General”.

(18) Concomitant medications

Drug code, the principal drug name: arrange concomitant medications for Crohn's disease (the concomitant medications checked at the indication: Crohn's disease in the survey form) per patient in the order of separate volume and description, and choose the concomitant medication data at the top. If there is no concomitant medication, leave the drug code column blank, and the name of the primary drug “null”.

Number of descriptions: count the number of the drug codes for concomitant medications arranged with the rule mentioned above. If more than 1 identical drug code is found in a patient, count it as 1 (for all the concomitant medications no matter whether the indication: Crohn's disease is checked). Describe “0” for the case with no concomitant medications.

(19) Effectiveness level

Follow Time Allowance of “12.1 Assessment period for CDAI, WPAI, CRP and no-intestinal conditions” to display remission/non-remission at the final assessment. Of note, if remission/non-remission at the final assessment is not reported, regard it as “unknown”.

(20) Adverse reactions

Handle the events with the identical PT code in a patient as 1 record regarding adverse events which occurred in the safety analysis period.

Organ-name code: select the SOC code. When presence/absence is “absence”, leave the column blank.

Adverse reaction code: select the PT code. When presence/absence is “absence”, leave the column blank.

Name of adverse reactions: select the PT. When presence/absence is “absence”, leave the column

blank.

Presence/absence: Select “present” for the data with both adverse events and causal relationship among the adverse reactions which occurred in the safety analysis period. If presence/absence of adverse events is unknown, select “unknown”. If presence/absence of adverse events is not provided, select “not provided”. Others are “absent”. If the reason is ‘safety assessment cannot be made’ in the patients excluded from the safety analysis, select “unknown”.

Number of descriptions: count the number of PT codes. If more than 1 identical PT code is found in a patient, count the PT as 1.

When presence/absence is “absence”, leave the column blank.

(21) Outcome

For PT codes displayed for adverse reactions, select the outcome with the highest priority in the “outcome” priorities defined in “10.2 Safety analysis”. When presence/absence of adverse reactions is “absence”, leave the column blank.

(22) Survey form number

Use the case number in this study.

(23) Dropout

If a patient is dropped out from both the safety analysis and the effectiveness analysis, display the case as “both_dropout”.

If a patient is dropped out only from the safety analysis, display the case as “Safe_dropout”.

“If a patient is dropped out only from the effective analysis, display the case as “Effective_dropout”.

Note: If there are no applicable data in an aggregation column, display “0” and no columns should be left blank.

“2.4.1.1 A list of the onset status of adverse reactions (priority survey items)”

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the summary statistics on the days to the onset as well as the number of patients per outcome and the days to the confirmed outcome (recovered or recovering) for adverse reactions of the priority survey items.

Analysis items: calculate the number of cases and the percentage to the number of patients in the analysis groups per type of adverse reactions (priority survey item, PT), and the number of patients with serious reactions and the percentage to the number of patients in the analysis groups regarding the adverse reactions which occurred in the safety analysis period. In addition, calculate the summary statistics (the number of patients, the mean, the minimum, the median, the maximum) for days to the onset per PT and priority survey item (for the total number of PTs) and for days from the onset date to the outcome (recovered or recovering) as well as the number of patients per outcome.

Note: When more than one identical PT is found in a patient, aggregate seriousness, days to the onset, outcome and days to the outcome (recovered or recovering) as 1 patient (case) in the following manner.

- Seriousness priority: serious > non-serious
- Days to the onset: identify the days as mentioned in "10.2 days from the first administration date of Humira to the adverse-event onset date".
- Outcome: identify it as mentioned in "10.2 Outcome".
- Days to outcome (recovered or recovering): identify the days as mentioned in 10.2 Days from an onset date of adverse events to the outcome confirmation date (recovered or recovering).

"2.4.1.2 A list of the onset status of adverse events (priority survey items)"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the summary statistics on the days to the onset as well as the number of patients per outcome and the days to the confirmed outcome (recovered or recovering) for adverse events of the priority survey items.

Analysis items: calculate the number of cases and the percentage to the number of patients in the analysis groups per type of adverse events (priority survey item, PT), and the number of patients with serious events and the percentage to the number of patients in the analysis groups regarding the adverse events which occurred in the safety analysis period. In addition, calculate the summary statistics (the number of patients, the mean, the minimum, the median, the maximum) for days to the onset per PT and priority survey item (for the total number of PTs) and for days from the onset date to the outcome (recovered or recovering) as well as the number of patients per outcome.

Note: When more than one identical PT is found in a patient, aggregate seriousness, days to the onset, outcome and days to the outcome (recovered or recovering) as 1 patient (case) in the following manner.

- Seriousness priority: serious > non-serious
- Days to the onset: identify the days as mentioned in "10.2 days from the first administration date of Humira to the adverse-event onset date".
- Outcome: identify it as mentioned in "10.2 Outcome".
- Days to outcome (recovered or recovering): identify the days as mentioned in 10.2 Days from an onset date of adverse events to the outcome confirmation date (recovered or recovering).

"2.4.2 A list of the onset status of the priority survey items per 100 patient-year"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the onset status of the priority survey items per 100 patient-year by adverse event, serious adverse event, adverse reaction, serious adverse reaction of patients in the safety analysis group.

Analysis items: calculate the number of patients and the percentage to the number of patients in the analysis groups per type of seriousness and type of priority survey items for adverse events/reactions which occurred between the first administration date of Humira and the final administration date of Humira + 28.
In addition, calculate the number of events/reactions and the event rate per 100 patient-year.

Note: Aggregate the total number of developed events/reactions including the overlapped ones which occurred in a patient.

"2.5.1 A list of the onset status of adverse reactions with/without self-administration"
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of adverse reactions with/without self-administration
Analysis item: aggregate the following items with/without self-administration for adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, etc. number of adverse reactions, type of adverse reactions, etc. (SOC, PT).

"2.5.2 A list of the onset status of adverse reactions with/without self-administration"
Patients for analysis: patients excluded from the safety analysis group
Analysis objective: to show the onset status of adverse reactions with/without self-administration
Analysis item: aggregate the following items with/without self-administration for adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, etc. number of adverse reactions, type of adverse reactions, etc. (SOC, PT).

"2.6 Incidence of adverse reactions per onset period (serious)"
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of serious adverse reactions per the onset period.
Analysis item: aggregate the following items by period for adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with serious adverse reactions, etc. number of serious adverse reactions, type of adverse reactions, etc. (SOC, PT).

Note: Aggregate the initial reactions among the identical PTs in a patient. Aggregate the events based on the segments which contain the initial onset period of adverse reactions among Time Allowance

defined in “12.4 Assessment period for the onset status of adverse reactions”. When calculating the number of patients with the target reactions, remove overlapped data per case number and onset period. When calculating the number of SOC, remove the overlapped data per case number, onset period and SOC.
Count the number of target patients and reactions by using the dates defined below until the assessment period applicable to Time Allowance defined in “12.4 Assessment period for the onset status of adverse reactions”.

- Discontinued patients: the final administration date of Humira + 28 days
- Not discontinued patients: the first administration date of Humira + 1120 days

Even if there is one adverse reaction, it should be counted as one patient in every period when the reaction persisted.

“2.7 Incidence of adverse reactions per set period”

Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of adverse reactions per onset period.
Analysis item: aggregate the following items by period for adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, etc. number of adverse reactions, type of adverse reactions, etc. (SOC, PT).

Note: Aggregate the initial reactions among the identical PTs in a patient. Aggregate the events based on the segments which contain the initial onset period of adverse reactions among Time Allowance defined in “12.4 Assessment period for the onset status of adverse reactions”. When calculating the number of patients with the target reactions, remove overlapped data per case number and onset period. When calculating the number of SOC, remove the overlapped data per case number, onset period and SOC.
Count the number of target patients and reactions by using the dates defined below until the assessment period applicable to Time Allowance defined in “12.4 Assessment period for the onset status of adverse reactions”.

- Discontinued patients: the final administration date of Humira + 28 days
- Not discontinued patients: the first administration date of Humira + 1120 days

Even if there is one adverse reaction, it should be counted as one patient in every period when the reaction persisted.

“2.9 Incidence of adverse reactions (serious adverse reactions/adverse reactions) per background factor”

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the incidence of adverse reactions per patient background factor and analyze them.

Analysis items: calculate the number of all patients, the percentage to the number of patients with serious adverse reactions and all patients, the number of patients with adverse reactions and the percentage to number of all patients, the tests for adverse reactions (Fisher's exact test for nominal-scale factors and Man-Whitney's u test for ordinal-scale factors) per the following patient background factor regarding the adverse reactions which occurred in the safety analysis period. Note that the test does not include the patients "with treatment history with anti-TNFα drug for Crohn's disease".

Note: the patient background factors are as follows:

Sex, age (year), body weight (kg), BMI (kg/m^2), duration of illness (year), indication (registration form), allergy history, smoking history, with smoking history (details), self-administration, tuberculosis test status, hepatitis B virus test status (registration form), complication, complication: liver disorder, complication: renal disorder, complication: blood disorder, complication: respiratory disorder, complication: diabetes mellitus, complication: osteoporosis, complication: malignant tumour, medical history, medical history: tuberculosis, medical history: non-tuberculous mycobacteriosis, medical history: interstitial pneumonia, medical history: bronchitis bacterial, medical history: aplastic anaemia, medical history: pancytopenia, medical history: malignant tumour, prior medication for Crohn's disease, prior medication: anti-TNFα drug, prior medication: aminosalicylic acid drug, prior medication: corticosteroids, prior medication: immunosuppressant,prior medication: antibiotics, prior treatment for Crohn's disease, prior treatment: surgery, prior treatment: GCAP, prior treatment: enteral nutrition therapy, prior treatment: intravenous nutrition therapy, treatment history with anti-TNFα drug for Crohn's disease, with treatment history with anti-TNFα drug for Crohn's disease, concomitant medication, concomitant medication: aminosalicylic acid drug, concomitant medication: corticosteroids, concomitant medication: immunosuppressant, concomitant medication: antibiotics, concomitant therapy for Crohn's disease, concomitant therapy: surgery, concomitant therapy: GCAP, concomitant therapy: enteral nutrition therapy, concomitant therapy: intravenous nutrition therapy, site of disease: anus/perianal region, site of disease: rectum, site of disease: stomach/duodenum, site of disease: colon, site of disease: jejunum/ileum, intestinal complication, non-intestinal complication, work condition, CDAI when the administration was started, CRP

"2.9.xx Incidence of adverse reactions per background factor and seriousness"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the onset status of non-serious/serious adverse reactions per statistically-significant background factor based on the test results in 2.9.

Analysis item: aggregate the following items per background factor and seriousness for adverse reactions which occurred in the safety analysis period.

Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, incidence of the reactions, number of adverse reactions and type of adverse reactions (SOC, PT).

"2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the onset status of non-serious/serious adverse reactions with/without hepatic function disorder

Analysis item: aggregate the following items with/without hepatic function disorder per seriousness regarding the adverse reactions which occurred in the safety analysis period.

Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, incidence of the reactions, number of adverse reactions and type of adverse reactions (SOC, PT).

Note: Aggregate the most serious reaction among the identical PTs in a patient.

When calculating the number of patients with the target reactions, remove overlapped data per case number and seriousness. When calculating the number per SOC, remove the overlapped data per case number, seriousness and SOC.

"2.14.1 Incidence of adverse reactions with/without renal impairment and per seriousness"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the onset status of non-serious/serious adverse reactions with/without renal impairment

Analysis items: aggregate the following items with/without renal impairment per seriousness regarding the adverse reactions which occurred in the safety analysis period.

Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, incidence of the reactions, number of adverse reactions and type of adverse reactions (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness".

"2.15.1 Incidence of adverse reactions per seriousness in pediatrics and non-pediatrics"

Patients for analysis: patients in the safety analysis group

Analysis objective: to separately show the onset status of serious or non-serious adverse reactions in pediatrics and non-pediatrics.

Analysis items: aggregate the following items per seriousness in pediatrics and non-pediatrics

regarding adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, incidence of the reactions, number of adverse reactions and type of adverse reactions (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness".

"2.16.1 Incidence of adverse reactions per seriousness in the elderly and non-elderly patients"
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of non-serious/serious adverse reactions in the elderly and non-elderly patients.
Analysis items: aggregate the following items per seriousness in the elderly and non-elderly patients regarding adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, incidence of the reactions, number of adverse reactions and type of adverse reactions (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness".

"2.17.1 A list of the onset status of adverse reactions/infections in this survey"
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of adverse reactions and serious adverse reactions.
Analysis item: aggregate adverse reactions and serious adverse reactions regarding the following items based on the adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, etc. number of adverse reactions, incidence of adverse reactions, etc., and type of adverse reactions, etc. (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness" for serious adverse reactions.
Put * before the PT of unexpected events from "Precautions".

"2.17.2 A list of the onset status of adverse reactions/infections not in the follow-up period"
Patients for analysis: patients whose survey form was locked
Analysis objective: to show the onset status of adverse reactions and serious adverse reactions which occurred not in the follow-up period.
Analysis item: aggregate adverse reactions and serious adverse reactions regarding the following

items based on the adverse reactions which occurred not in the safety analysis period.

Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, etc. number of adverse reactions, incidence of adverse reactions, etc., and type of adverse reactions, etc. (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness" for serious adverse reactions.
Put * before the PT of unexpected events from "Precautions".

"2.17.3 A list of the onset status of adverse reactions/infections in this survey (patients excluded from the safety analysis)"

Patients for analysis: patients excluded from the safety analysis group
Analysis objective: to show the onset status of adverse reactions and serious adverse reactions.
Analysis item: aggregate adverse reactions and serious adverse reactions regarding the following items based on the adverse reactions which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, etc. number of adverse reactions, incidence of adverse reactions, etc., and type of adverse reactions, etc. (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness" for serious adverse reactions.
Put * before the PT of unexpected events from "Precautions".

"2.19 A list of the onset status of adverse events in this survey"

Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of adverse events, serious adverse events and non-serious adverse events.
Analysis items: aggregate adverse events, serious adverse events and non-serious adverse events regarding the following items among adverse events which occurred in the safety analysis period.
Calculate the number of patients and the percentage to the number of patients surveyed per number of patients surveyed, number of patients with adverse reactions, number of adverse reactions, incidence of the reactions, type of adverse events (SOC, PT).

Note: refer to the note of "2.13.1 Incidence of adverse reactions with/without hepatic function disorder and per seriousness" for serious adverse events.

"2.20 A list of the onset status of adverse reactions (all cases)"

Patients for analysis: patients in the safety analysis group
Analysis objective: to show the summary statistics on the days to the onset as well as the number of

patients per outcome and the days to the confirmed outcome (recovered or recovering) for adverse reactions.

Analysis items: calculate the number of cases and the percentage to the number of patients in the analysis groups per type of adverse reactions (SOC, PT), the number of patients with non-serious reactions and the percentage to the number of patients in the analysis groups, and the number of patients with serious reactions and the percentage to the number of patients in the analysis groups for the adverse reactions which occurred in the safety analysis period. In addition, calculate the summary statistics (the number of patients, the mean, the minimum, the median, the maximum) for days to the onset per PT, the number of patients per period from the onset date to the outcome (recovered or recovering), and the number of patients per outcome.

Note: When more than one identical PT is found in a patient, aggregate seriousness, days to the onset, outcome and days to the outcome (recovered or recovering) as 1 patient (case) in the following manner.

- Seriousness priority: serious > non-serious
- Days to the onset: identify the days as mentioned in "10.2 days from the first administration date of Humira to the adverse-event onset date".
- Outcome: identify it as specified in 10.2 Outcomes of adverse events
- Days to outcome (recovered or recovering): identify the days as mentioned in 10.2 Days from an onset date of adverse events to the outcome confirmation date (recovered or recovering).

13.3. Effectiveness

"3.1 CDAI remission rate at the final assessment (CDAI<150)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show the remission rate of CDAI at the final assessment

Analysis items: calculate the number of target patients, the percentage to the number of patients who achieved a remission at the final assessment and to the number of target patients, and the percentage to the number of patients who failed to achieve a remission and to the number of target patients.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods.

"3.2.1.1 Changes in Crohn's disease activity index (CDAI) since the administration was started (Observed Case)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show changes in CDAI and CDAI at each assessment period.

Analysis items: Calculate the number of target patients, the mean and standard deviation of CDAI,

the mean and standard deviation of changes in CDAI for each assessment period, and conduct a paired-t test which compares the values at the initial administration. In addition, calculate the mean days from the first administration date to the final assessment date and the ± standard deviation.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods. The analysis covers only the patients with the assessment at the first administration and thereafter.

"3.2.1.2 Changes in Crohn's disease activity index (CDAI) since the administration was started (Observed Case)"

Patients for analysis: the patients in the effectiveness analysis group whose CDAI was a remission (≥150) after they were started on Humira.

Analysis objective: to show changes in CDAI and the CDAI at each assessment period of patients whose CDAI failed to achieve a remission when the administration was started.

Analysis items: Calculate the number of target patients, the mean and standard deviation of CDAI, the mean and standard deviation of changes in CDAI for each assessment period, and conduct a paired-t test which compares the values at the initial administration. In addition, calculate the mean days from the first administration date to the final assessment date and the ± standard deviation.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods. The analysis covers only the patients with the assessment at the first administration and thereafter.

"3.2.2.1 Changes in the remission rate at each point (CDAI<150) (Observed Case)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show the remission rate of CDAI at each assessment period.

Analysis item: Calculate the number of target patients, the percentage to the number of patients who achieved a remission and the number of target patients, 95%CI of the remission rate, and conduct a McNemar test for the first administration per assessment period.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods. The analysis covers only the patients with the assessment at the first administration and thereafter.

For the confidence interval, use the Clopper-Pearson's confidence interval.

"3.2.2.3 Changes in the remission rate at each point (CDAI<150) (Observed Case)"

Patients for analysis: the patients in the effectiveness analysis group whose CDAI was a remission (≥150) after they were started on Humira.

Analysis objective: to show the remission rate of CDAI at each assessment period of patients whose CDAI failed to achieve a remission when the administration was started.
Analysis item: Calculate the number of target patients, the percentage to the number of patients who achieved a remission and the number of target patients, 95%CI of the remission rate, and conduct a McNemar test for the first administration per assessment period.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods. The analysis covers only the patients with the assessment at the first administration and thereafter.
For the confidence interval, use the Clopper-Pearson's confidence interval.

"3.2.4.2 Endoscopy results during administration (small intestine: active phase/remission phase)"

Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show endoscopy results (small intestine) at each assessment period.
Analysis item: Calculate the number of patients who did not undergo endoscopy, the number of patients who underwent endoscopy, the percentage to the number of patients in the active phase and the number of patients who underwent endoscopy, the percentage to the number of patients in the remission phase and the number of patients who underwent endoscopy, and the mean days from the endoscopy prior to administration to the first administration date of Humira.

Note: Follow "12.2 Assessment period for endoscopy results" for Time Allowance of assessment period. The analysis covers only the patients with the endoscopy assessment (small intestine) at the first administration and thereafter in the effectiveness analysis group.

"3.2.5.2 Endoscopy results during administration (large intestine: active phase/remission phase)"

Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show the endoscopy results (large intestine) at each assessment period.
Analysis item: Calculate the number of patients who did not undergo endoscopy, the number of patients who underwent endoscopy, the percentage to the number of patients in the active phase and the number of patients who underwent endoscopy, the percentage to the number of patients in the remission phase and the number of patients who underwent endoscopy, and the mean days from the endoscopy prior to administration to the first administration date of Humira.

Note: Follow "12.2 Assessment period for endoscopy results" for Time Allowance of assessment period. The analysis covers only the patients with the endoscopy assessment (large intestine) at the first administration and thereafter in the effectiveness analysis group.

"3.2.5.3 Endoscopy results during administration (remission phase in both small and large intestines)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show endoscopy results in the remission phase (for small and large intestines)

Calculate the number of patients who underwent endoscopy (for small and large intestines), the number of patients whose small and large intestines in the remission phase, and the percentage to the patients who underwent endoscopy (for small and large intestines).

Note: Follow "12.2 Assessment period for endoscopy results" for Time Allowance of assessment period. The analysis covers only the patients with the data showing that endoscopy for small and large intestines was done on the same day at the first administration and thereafter in the effectiveness analysis group.

"3.2.6.2 Changes in WPAI:CD since the administration was started (Observed Case)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show WPAI at each assessment period.

Analysis items: Calculate the number of target patients and the summary statistics of WPAI for each assessment period, and conduct a paired-t test which compares the values at the initial administration.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods. The analysis covers only the patients with the WPAI assessment at the first administration and thereafter in the effectiveness analysis group.

"3.2.7.2 Changes in CRP level since the administration was started (Observed Case)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show CPR levels at each assessment period.

Analysis items: Calculate the number of target patients and the summary statistics of CRP for each assessment period, and conduct a paired-t test which compares the values at the initial administration.

Note: Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the final assessment periods. The analysis covers only the patients with the CRP assessment at the first administration and thereafter in the effectiveness analysis group.

"3.2.7.3 Remission rate at the final assessment in patients who achieved a remission of CDAI at Week 4 of administration"

Patients for analysis: Patients in the effectiveness analysis group (the patients who did not achieve a remission (≥150) when the administration was started but achieved the remission (<150) at Week 4 of administration in CDAI)

Patients for analysis: to show the remission rate of CDAI at the final assessment regarding the patients who did not achieve a remission (≥150) when the administration was started but achieved the remission (<150) at Week 4 of administration.

Analysis items: calculate the number of target patients, the percentage to the number of patients who achieved a remission at the final assessment and the target patients, and the 95% confidence interval of the remission rate.

Note: The target patients need to have their CDAI measured at 3 time points or more, that is, at the first administration, Week 4 of administration and any point after Week 4 of administration and also have a record that they did not achieve a remission (≥150) at the first administration but achieved the remission (<150) at Week 4 of administration.

Follow "12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions" for Time Allowance of the assessment periods.

For the confidence interval, use the Clopper-Pearson's confidence interval.

"3.2.8 Subsequent changes in the conditions of patients with non-intestinal conditions observed at the first administration (Observed Case)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show the conditions at each assessment period regarding non-intestinal conditions observed at the first administration.

Analysis item: Calculate the number of target patients, the percentage to the number of patients with the conditions and the number of target patients, and conduct a McNemar test for the first administration per assessment period.

Note: The analysis covers only the patients with the assessment at the first administration and thereafter as well as the patients with symptoms for each "arthritis/arthralgia", "iritis/uveitis", and "erythema nodosum/gangrenous abscess/aphthous stomatitis" at the first administration.

To analyze "with any of non-intestinal conditions", the patients with any symptom at each assessment period regarding any of the items answered as 'with a symptom' at the first administration are regarded as the patients with conditions. When a patient had multiple symptoms at the first administration, they should be regarded as "with conditions" if any of the symptoms persisted. Do not include in analysis the items in which no symptoms were observed at the first administration. (Do not include in the analysis a symptom which first developed at an assessment

period after the first administration, either)
Follow “12.1 Assessment period for CDAI, WPAI, CRP and non-intestinal conditions” for Time Allowance of the assessment periods.

“3.4.1 Aggregation for effectiveness per patient background factor (CDAI)”
Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show the CDAI remission rate at the final assessment per patient background factor and analyze them.
Analysis items: For CDAI at the final assessment, calculate the number of patients, the percentage to the number of patients who failed to achieve a CDAI remission and the number of patients per background factor, the number of patients who achieved a CDAI remission and the percentage to the number of patients per background factor, and the tests for CDAI remission (Fisher’s exact test for nominal-scale factors and Man-Whitney’s u test for ordinal-scale factors) per patient background factor below. Note that the test does not include the patients “with treatment history with anti-TNFα drug for Crohn’s disease”.
Note: the patient background factors are as follows:
Sex, age (year), body weight (kg), BMI (kg/m^2), duration of illness (year), indication (registration form), allergy history, smoking history, with smoking history (details), self-administration, tuberculosis test status, hepatitis B virus test status (registration form), complication, complication: liver disorder, complication: renal disorder, complication: blood disorder, complication: respiratory disorder, complication: diabetes mellitus, complication: osteoporosis, complication: malignant tumour, medical history, medical history: tuberculosis, medical history: non-tuberculous mycobacteriosis, medical history: interstitial pneumonia, medical history: bronchitis bacterial, medical history: aplastic anaemia, medical history: pancytopenia, medical history: malignant tumour, prior medication for Crohn’s disease, prior medication: anti-TNFα drug,prior medication: aminosalicylic acid drug, prior medication: corticosteroids, prior medication: immunosuppressant, prior medication: antibiotics, prior treatment for Crohn’s disease, prior treatment: surgery, prior treatment: GCAP, prior treatment: enteral nutrition therapy, prior treatment: intravenous nutrition therapy, treatment history with anti-TNFα drug for Crohn’s disease, with treatment history with anti-TNFα drug for Crohn’s disease, concomitant medication, concomitant medication: aminosalicylic acid drug, concomitant medication: corticosteroids,concomitant medication: immunosuppressant, concomitant medication: antibiotics, concomitant therapy for Crohn’s disease, concomitant therapy: surgery, concomitant therapy: GCAP, concomitant therapy: enteral nutrition therapy, concomitant therapy: intravenous nutrition therapy, site of disease: anus/perianal region, site of disease: rectum, site of disease: stomach/duodenum, site of disease: colon, site of disease: jejunum/ileum, intestinal complication, non-intestinal complication, work condition, CDAI when the administration was started, CRP