Humira® for subcutaneous use only

Special drug-use survey

-Long-term survey on Colitis ulcerative-

Statistical Analysis Plan (the 6th periodical safety report/re-examination/final report)

Version 2.1

Prepared in 2018 March 12

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1. Preparation/revision history

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
1.0	February 6, 2017	Yutaro Shiraishi	First version
1.1	May 23, 2017	Yutaro Shiraishi	■ General ● Names of external files were amended for re-examination ■ 2. Definitions of terms and abbreviations ● The definitions of “adverse events in the safety analysis period” and “adverse events not in the safety analysis period” were changed ■ 6. Presence/absence of analysis and its schedule ● the 7th periodical safety report was deleted. ■ 8. Definitions of groups used for analysis ● The definition of “registered patients” was changed, and the definitions of “patients ineligible for registration”, “patients with registration pending” and “patients eligible for registration” were deleted. ● The definitions of “patients whose survey form was locked” and “patients whose survey form was yet to be locked” were changed. ● The definition of “patients excluded from the effective analysis group” was partly deleted. ■ 10.1 General ● The definition of “reasons for change in dose/dosing frequency” was changed. ● Descriptions of “presence of

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
			complications", "presence of medical history", "presence of complication/others" and "presence of medical history/others" were amended for clarification ● The definitions of "HBs antigen test", "HBs antibody test", "HBc antibody test", "HBV-DNA quantification test" and "Tuberculin test or IGRA test" were changed ● The definitions of "Chest X ray or CT test", "tuberculosis test" and "Hepatitis B test" were added ● "To describe the drug name" was added to the definitions of "presence of prior medication" and "presence of concomitant medication" ■ 11. How to stratify data ● "Circulatory disorders" was deleted in "Detailed classification of complications" ● "Gastrointestinal disorder" and "Collagen disorder" were deleted in "Other classifications of complications" ● "Presence of decreased response", "acute events", "delayed events" and "Unknown/Not provided" were deleted in "Detailed classification of 'using' biological products" ■ 13.1 General ● Analysis items of 1.1, 1.3.1, 1.4 and 1.4.1 were changed ● 1.4.4 was added ● Analysis target in 1.7 and 1.13 was changed ● Analysis target and items were

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
			changed in 1.12. ● Analysis target in 3.6 was changed and the table number was also changed to 1.6.2 ■ 13.2 Safety ● Analysis items of 2.4.1, 2.4.2, 2.4.3, 2.4.4, 2.9 and 3.4 were changed ● 2.5.1, 2.9.xx, 2.18.1 and 2.19 were added. ● Remarks were added in 2.6 ● Analysis target, analysis objective and analysis items were changed in 3.4.1.
2.0	February 6, 2018	Yutaro Shiraishi	■ General ● Names of external files were amended for final report ■ 6. Presence/absence of analysis and its schedule ● Final report period was added ■ 7.2. Dictionary in use ● MedDRA/J version update ■ 8. Definitions of groups used for analysis ● Exclusion items for “patients excluded from the efficacy analysis group” were added. ■ 9.3. Digits displayed for figures ● Descriptions on CRP were added ■ 10.1 General ● The definition of “Administration status (dosage and administration)” was amended. ● “Reasons for discontinuation/other reasons”, “detailed classification of smoking history”, “presence of prior medication (azathioprine &

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
			6-mercaptopurine)", "presence of prior medication (tacrolimus & ciclosporin)", "presence of combination drug (azathioprine & 6-mercaptopurine)", and "presence of combination drug (tacrolimus & ciclosporin)" were newly added. ● The description of "presence of smoking history" was amended for clarification. ● The conditions for drug code were added in "presence of prior medication" and "presence of presence of concomitant medication" ● "Presence of prior medication (aminosalicylic acid drug)", "presence of prior medication (corticosteroids)", "presence of prior medication (azathioprine)", "presence of prior medication (6-mercaptopurine)", and "presence of prior medication (antibiotics)", were added for the conditions of the survey form. ● The condition of ciclosporin was added in "presence of prior medication (others)" and "concomitant medication (others)". ■ 10.3 Effectiveness analysis ● "Responder of partial Mayo score" was newly added ● Endoscopy results were added ■ 11. How to stratify data ● "Reasons for discontinuation/other reasons", "detailed classification of smoking history" and "disease site per type" were newly added.

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
			● Azathioprine & 6-mercaptopurine were added and tacrolimus was replaced with tacrolimus & ciclosporin in “detailed classification of prior medications for colitis ulcerative” and “detailed classification of concomitant medications for colitis ulcerative” ● “Unknown/Not provided” was added in the discontinuation reason for the detailed classification of ‘using’ biological products”. ● “Normal or remission-phase mucosa, mild, moderate, severe in severity” was added in “endoscopy results” ■ 12.3 Assessment period of Mayo score ● The definitions of the time of discontinuation and the time of final assessment were added. ■ 12.4 Assessment period of partial Mayo score ● Time point was added ■ 12.6 Assessment period of CRP ● Time point was added ■ 12.7 Assessment period for the continued administration of Humira ● Time point was added ■ 13.1 General ● Analysis items of 1.4, 1.4.1, 1.4.4 and 1.12 were changed ● Analysis target was changed in 1.6.2 ● Aggregation details was changed in 1.7.1 ■ 13.2 Safety ● The period classification was changed in 2.1

Version No.	Date of preparation/revision	Prepared/revised by	Reasons
			● Analysis items were changed in 2.9 and 2.20 ■ 13.3 Effectiveness ● 3.1.5.2, 3.1.7.2, 3.6 and 3.7 were newly added ● Analysis details was changed in 3.1.7.1 and 3.4 ● Analysis objective was changed in 3.4 ● Analysis item was changed in 3.5 ● Analysis target and objective were changed in 3.4.1
2.1	March 12, 2018.	Yutaro Shiraishi	■ 11. How to stratify data ● “Partial Mayo score” was changed Changed from “≥6 and <9” to “≥6 and ≤9”

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 56 of administration (Day 1 + 392) Note that adverse events in discontinued cases should be the ones which occur from the first administration date of Humira through the final administration + 28 days.
Adverse events not in the safety analysis period	Adverse events which occur prior to the first administration date of Humira or beyond Week 56 of administration (Day 1 + 392). Note that adverse events in discontinued cases should be the ones which occur prior to the first administration date of Humira or beyond the final administration + 28 days.
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.
Summary statistics	It includes number of cases, mean, standard deviation, minimal value, 1st quartile value, median, 3rd quartile value and maximal value.
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
IGRA test	Interferon gamma release assay
Partial Mayo score	Total of stool frequency sub score, rectal bleeding sub score and physician’s global assessment
Mayo score	Total of partial Mayo score and endoscopy score
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 colitis ulcerative)" (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

This survey aims at exploring the following items in colitis ulcerative patients who used Humira, as the special drug-use survey of Humira ® for subcutaneous use only (the long-term survey).

1) Unexpected adverse reactions (Specifically important adverse reactions)
2) The onset status of adverse reactions in the practical use
3) Factors which may affect the safety and effectiveness

<Priority survey items>

The onset status of infection, tuberculosis, malignant tumour, administration site reactions, autoimmune disease, pancytopenia, demyelinating disease, cardiac failure congestive and interstitial pneumonia

If an intestinal infection occurs, investigate the virus or bacterium causing it whenever possible.

4.2. Survey plan

The patients should have colitis ulcerative in the active moderate or severe phase (only when an existing treatment does not work) and newly receive Humira.

4.3. Target sample size for the survey

1500 patients

<Rationale for the sample size>

1. As this survey is conducted in the clinical settings, we expect that the patients with a treatment history with anti-TNFα drugs may be highly observed. Given that the registration of such patients can increase the dropout rate compared to that of the relevant domestic clinical studies, we calculated that the dropout rate would reach 70% at Week 52. Next, given that the number of patients whose CDAI of the effectiveness endpoint was not

provided in the all-case survey for Crohn's disease accounted for approximately 30%, we need 1500 patients with 30% remission rate, ±5% estimated accuracy of 95% CI and under the conditions where 30% of Mayo score are not assessable (Table 1).

Table 1: The number of patients and accuracy calculated based on the dropout rate

Dropout rate 70%				
Sample size	After Week 52 Sample size	Mayo score Number of patients for assessment	At Week 52 Remission rate 30% 95%CI	Accuracy
500	150	105	21.2-38.8	±8.8%
1000	300	210	23.8-36.2	±6.2%
1500	450	315	24.9-35.1	±5.1%
2000	600	420	25.6-34.4	±4.4%

The number of cases with Mayo score provided was calculated as 70% of the total number of patients after Week 52 (i.e., 30% of Mayo score is not provided).

2. Next, we examined the accuracy of the remission rate where the number of patients was 1500 as mentioned above with/without treatment experience of anti-TNFα drugs (Table 2). We set the following conditions for the accuracy examination:

The all-case survey data in Crohn's-disease patients who used Humira showed that 80% of the patients had been treated with anti-TNFα drugs while 20 % had not. Given that there were many patients who could not benefit from an anti-TNFα agent of prior medication awaiting right after the indication of Crohn's disease was approved, we expect that the same percentage of patients can be enrolled in this survey, too. In this regard, we decided to adopt the similar ratio for the anti-TNFα drug use in this survey and have the patients with and without the treatment history of the drug in an 8:2 ratio.

We set the remission rate of Mayo score at Week 52 in the patients without anti-TNFα drug history as 30% based on the percentage used to estimate the above 1500 patients and in the patients with the history as 10% based on the data in an overseas clinical study (M06-827 Study).

Table 2: The Accuracy of remission rate with/without treatment history of anti-TNFα drugs

	Mayo score Number of patients for assessment	At Week 52 Remission rate	95%CI	Accuracy
With a treatment history of anti-TNFα drugs	252	10%	6.1-13.9	±3.8%
Without a treatment history of anti-TNFα drugs	63	30%	17.9-42.1	±12.1%

These results suggest that the value might be less accurate due to a fewer number of patients in the group of no treatment history of anti-TNFα drugs while the value in the group with the treatment history will be accurate enough for the examination. (Table 2)

3. For the safety, tuberculosis occurred in a patient (1/177 patients, 0.6%) as an important adverse event (the causal relationship with Humira: probably not related) in a relevant domestic clinical study. If data from 1500 patients are collected based on the incidence, we can assess the accuracy with the 95%CI for the incidence of 0.3%-1.1%. Even if the incidence of tuberculosis reached 2% in this survey, which is higher than that of the clinical study, the confidence interval would range between the minimum 1.35 and the maximum 2.84 by collecting 1500 patients. In this case, the incidence of tuberculosis (as an adverse event) observed in a clinical study for arthritis rheumatoid exceeds 1.0%, meaning that the accuracy is assessable.

Therefore, we have 1500 patients as the target sample size.

5. Items to be analyzed and the methods

5.1. Analysis items

1) Items regarding patient composition
   - [1] Sample size for registration
   - [2] The number of patients whose survey form was locked
   - [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/infections
   - [2] Factors which may affect the safety
     - Incidence of adverse reactions per patient background, etc.
     - Presence/absence of the experience with biological products, and the relation with it
     - Safety for long-term use
     - Safety relationship when anti-adalimumab antibody was measured
     - Presence/absence of self-administration and the relation with it
   - [3] Adverse events which occurred during or after the administration
     - A list of the onset status of serious adverse events, etc.
     - The onset status of intestinal infection of cytomegalovirus colitis
   - [4] Warnings, Careful Administration section, and major adverse events subject to

special attention in Important Precautions section in Humira's package insert (infections including tuberculosis, malignant tumour, injection site reactions, allergic reaction, demyelinating disorders, lupus-like syndrome and blood disorder)

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

[6] The safety in pediatric patients with colitis ulcerative

3) Items regarding effectiveness

- Changes in the effectiveness until Week 52 of administration (Mayo score, partial Mayo score, etc.)
- Presence/absence of the experience with biological products, and the relation with it
- Effectiveness per prior medication history
- Effectiveness for long-term use (including the percentage of the secondary failure)
- Effectiveness relationship when anti-adalimumab antibody was measured
- Effectiveness in pediatric patients with colitis ulcerative

4) Items regarding patients with special backgrounds

A list of onset status of adverse reactions/infections in patients with special backgrounds such as pediatrics, the elderly, pregnant woman, renal impairment, hepatic function disorder, 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
The 6th periodical safety report	January 1, 2016 to December 31, 2016
Re-examination	June 14, 2013 to May 15, 2017
Final report	June 14, 2013 to March 31, 2018

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 should be used for aggregation, 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
Registered patients	The patients assessed as eligible for registration
Patients whose survey form was locked	Registered patients whose survey form was locked.
Patients whose survey form was yet to be locked	Registered patients whose survey form was yet to be locked. See Reference Data “Survey form lock/unlock information” for the criteria for the status that a survey form is 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 Reference Data “Inclusion/exclusion of patients” for the criteria to exclude patients from the safety analysis group. The exclusion items are as follows: ・ Breach of contract: unsigned institutions/specialties ・ Breach of contract: an excess of contracted number of patients ・ Breach of contract: unsigned physicians ・ Not treated with Humira ・ Not confirmed by physician ・ Overlapped patients ・ Safety is not assessable ・ Breach of registration criteria: a deviation from the registration period ・ Breach of registration criteria: with a history of treatment with Humira ・ Administration prior to contract ・ Data credibility cannot be confirmed: closure/merger of medical institutions ・ Data credibility cannot be confirmed: the physician was transferred ・ Data credibility cannot be confirmed: the physician refuses confirmation ・ Data credibility cannot be confirmed: inconsistency was found in the survey form
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	The patients who satisfy the exclusion criteria for the effectiveness analysis group. See Reference Data “Inclusion/exclusion of patients” for

Name of group	Definition
group	the exclusion criteria for the effectiveness analysis group. The exclusion items are as follows: ・ Breach of registration criteria: Not the disease to be surveyed ・ Effectiveness is not assessable
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

No missing data at any time are imputed for analysis. Note that entry data need to be imputed in some items and the imputation method for imputation-required items is defined in the definitions of each item at Chapter 10 or thereafter.

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" and "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	Number of patients, mean, standard deviation, median, minimal value, maximal value, etc.

9.3. Display digit for figures

The display digit for figures is as follows:

Type of figure	Display digit
Mean, standard deviation, median	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, 95% Confidence Interval	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. When adjusting multiplicity, describe it in each chart of Chapter 13.

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 site	If the same code is found among the DCF codes of "[Humira UC]DCF code list_Company A" "[Humira UC]DCF code list_Company E", it should be regarded as 1 site.
Number of patients per site	The number of patients are calculated per the identical DCF site code.
Patients with an adverse event which occurred not in the safety analysis period	Patients with at least one adverse event which occurred not in the safety analysis period
Patients who developed an infection	Patients with at least one event which is categorized into infection in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed tuberculosis	Patients with at least one event which is categorized into tuberculosis in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed malignant tumour	Patients with at least one event which is categorized into malignant tumour in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed an administration site reaction	Patients with at least one event which is categorized into administration site reaction in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed an autoimmune disease	Patients with at least one event which is categorized into auto-immune disease in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed pancytopenia	Patients with at least one event which is categorized into pancytopenia in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed demyelinating disease	Patients with at least one event which is categorized into demyelinating disease in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed cardiac failure congestive	Patients with at least one event which is categorized into cardiac failure congestive in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients who developed interstitial pneumonia	Patients with at least one event which is categorized into interstitial pneumonia in the "Priority Survey Item List_MedDRA20.1_FIX".
Patients subject to AAA measurement	Patients who are described in "UC Survey AAA Measurement (final report)".

Data name	Derivation and calculation methods
Patients of contraindications	The patients whose registration form has at least a check on the checkbox of contraindications.
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 + 364 days (Week 52) < 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] Impute the first administration date of each data on the final dates of the first and second administrations. [3] If the final date is described for the third administration and thereafter, 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 for the third administration and thereafter, 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 + 364 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. [4] Even though the final dates of the third administration and thereafter are described, but the final administration date is not 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

Data name	Derivation and calculation methods
	administration date. If the next record has already been generated and the first administration date of the next record comes earlier than the date imputed as the final date of the year, impute the first administration date of the next 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 + 364 days < the final administration date of Humira imputed according to the above rule, select the first administration date of Humira + 364 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
Administration status (dosage and administration)	Sort the data by the first administration date provided in "the administration status of Humira" in the survey form and aggregate the administration status (dosage and administration) according to the following rules: ・If all the following [1] to [4] are satisfied, aggregate the data as "160mg→80mg→40mg once every two weeks and no changes thereafter". ・If none of the following [1] to [4] is satisfied Aggregate as "others". [1] 1st administration: as a patient with a dose of 160mg

Data name	Derivation and calculation methods
	[2] 2nd administration: as a patient with a dose of 80mg [3] 3rd 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 third administration and thereafter, all the administration status should be the condition as shown in [3]. [4] Patients who did not have a washout period for 30 days or longer.
Reason for change in dose/dosing frequency	If the administration status (dose and administration) is categorized in "others", follow the rules below to find the reason for the change in dose/dosing frequency. ・1st dose: "a reason for other than 160mg (a dose) or in the case of self-administration" in the survey form. ・2nd dose: "a reason for other than 80mg (a dose) or in the case of self-administration" in the survey form. ・3rd and the subsequent dose(s): "a reason for other than 40mg (a dose), or in the case of other than once every 2 weeks (dosing frequency)" or "reason for change in dose/dosing frequency" in the survey form.
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 ・The interval between first and second administrations should be 14 days. ・For the third and subsequent dose(s), the interval should be 14 days if the dosing frequency "once every 2 weeks" is checked while the dosing frequency should be obtained from "[Humira UC] Conversion data provided for analysis" if the dosing frequency is "others". [3] Calculate the dosing frequency per data on administration status. Dosing frequency = (the final administration date (after imputed) – the first administration date(after imputed))/dosing

Data name	Derivation and calculation methods
	frequency (number of days) [4] When the results of [3] are “>0” (bigger than 0) and “<1” (smaller than 1), the dosing frequency shall be counted 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] If “Others” of a Humira dose is checked, the dose should be obtained from “[Humira UC] Conversion data provided for analysis”. [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 daily dose The mean daily dose = the total dose/the total number of dosing
Discontinued patients	If a patient’s final administration date of Humira comes before the first administration date of Humira + 336, we handle the patient as a discontinued case. Follow the above definition, no matter whether the discontinuation is selected in the survey form.
Presence/absence of reason for discontinuation	“Present” is defined for the situation where a patient qualifies for the defined discontinued case and at least one has been checked in “reason for discontinuation” of “discontinuation of the survey” of the survey form. On the other hand, if a patient qualifies for the defined discontinued case and no description has been made in the “reason for discontinuation” column in the survey form, the case is defined as an “unknown/not provided” case.
Reason for discontinuation	It should derive from “reason for discontinuation” of “discontinuation of the survey” of the survey form. Recode the reason for discontinuation based on other descriptions of “reason for discontinuation” and “[Humira UC] Conversion data provided for analysis”. Select “unknown/not provided” for undescribed data”.
Reason for discontinuation, other reasons	Obtain the detailed items of reason for discontinuation “others” in “[Humira UC] Conversion data provided for analysis”.
Patients who continue	The patients who are not the discontinued cases are regarded as the

Data name	Derivation and calculation methods
the survey	patients who continue the survey
Presence/absence of complications	When complication data are contained in the survey form, it should be classified as “with complications”. When there is no description of “presence/absence of complications” in the survey form or the assessment is impossible, it should be classified as “unknown/not provided”, and other cases are “no complications”.
Presence/absence of medical history	When medical-history data are contained in the survey form, it should be classified as “with medical history”. When there is no description of “presence/absence of medical history” in the survey form or the assessment is impossible, it should be classified as “unknown/not provided”, and other cases are “no medical history”.
Complication/Hepatic function disorder	When hepatic function disorder data are contained in “171210 Complication”, it should be classified as “with hepatic function disorder”. other cases are “no hepatic function disorder”.
Complication/Renal impairment	When renal impairment data are contained in “171210 Complication”, it should be classified as “with renal impairment”. other cases are “no renal impairment”.
Presence/absence of Complication/Circulatory disorder	When circulatory disorder data are contained in “171210 Complication”, it should be classified as “with circulatory disorder”. other cases are “no circulatory disorder”.
Presence/absence of Complication/Blood disorder	When blood disorder data are contained in “171210 Complication”, it should be classified as “with blood disorder. Other cases are “no disorder”.
Presence/absence of Complication/Respiratory disorder	When respiratory disorder data are contained in “171210 Complication”, it should be classified as “with respiratory disorder. Other cases are “no respiratory disorder”.
Presence/absence of Complication/others	If a survey form contains the data other than hepatic function disorder, renal impairment, circulatory disorder, blood disorder and respiratory disorder, it should be classified as “with other complications”. Others are “no other complications”. If a survey form contains the data in “171210 Complication” for presence/absence of diabetes mellitus, gastrointestinal disorder, osteoporosis and malignant tumour as well among the detailed classifications of other complications, it should be classified as “with complications”. Others are “no complications”.

Data name	Derivation and calculation methods
	If a survey form contains the data on complications other than diabetes mellitus, gastrointestinal disorder, osteoporosis and malignant tumour among the detailed classifications of other complications, it should be classified as “with other complication of other detailed classifications”. Others are “no other complication of other detailed classifications”. As for collagen disorder, if “other: collagen disorder” in “complications” of “patient information” is checked, it should be classified as “with collage disorder. Other cases are “no collagen disorder”.
Medical history: presence/absence of tuberculosis	When tuberculosis data are contained in “180111 Medical history”, it should be classified as “with tuberculosis. Other cases are “no tuberculosis”.
Medical history: presence/absence of non-tuberculous mycobacteriosis	When non-tuberculous mycobacteriosis data are contained in “180111 Medical history”, it should be classified as “with non-tuberculous mycobacteriosis. Other cases are “no non-tuberculous mycobacteriosis”.
Medical history: presence/absence of interstitial pneumonia	When interstitial pneumonia data are contained in “180111 Medical history”, it should be classified as “with interstitial pneumonia. Other cases are “no interstitial pneumonia”.
Medical history: presence/absence of bronchitis bacterial	When bronchitis bacterial data are contained in “180111 Medical history”, it should be classified as “with bronchitis bacterial. Other cases are “no bronchitis bacterial”.
Medical history: presence/absence of aplastic anaemia	When aplastic anaemia data are contained in “180111 Medical history”, it should be classified as “with aplastic anaemia. Other cases are “no aplastic anaemia”.
Medical history: presence/absence of pancytopenia	When pancytopenia data are contained in “180111 Medical history”, it should be classified as “with pancytopenia. Other cases are “no pancytopenia”.
Medical history: presence/absence of malignant tumour	When malignant tumour data are contained in “180111 Medical history”, it should be classified as “with malignant tumour. Other cases are “no malignant tumour”.
Medical history: presence/absence of other medical history	When medical-history data except tuberculosis, non-tuberculous mycobacteriosis, interstitial pneumonia, bronchitis bacterial, aplastic anaemia, pancytopenia and malignant tumour are contained among the medical-history data in the survey form, it should be classified as

Data name	Derivation and calculation methods
	"with other medical history". The remaining cases are "no other medical history".
Presence/absence of allergy history	When "with allergy history in "patient information" of the survey form is checked, it should be classified as "with allergy history. When "allergy history unknown" is checked, it should be "unknown" whereas nothing is provided in "presence/absence of allergy history" of the form, it should be "not provided". Other cases are "no allergy history".
Patients with an hepatitis B virus infection	When "Hepatitis→viral" is selected in "Complications" of "Patient information" in the survey form and also "B" is selected for "Hepatitis virus carrier", the patient is classified as a patient with an hepatitis B virus infection. The patients also include those developed an adverse event encoded with the applicable MedDRA PT described in "patients with 180111B Hepatitis B virus infection".
Presence/absence of smoking history	For the items for smoking history in the survey form, when the checkboxes of "smoking" or "in the past" are checked, or when "with smoking history" is checked and the smoking period is "unknown", both cases should be classified as "with smoking history". When "unknown" is checked for smoking history, it should be "unknown". When nothing is described in "presence/absence of smoking history" of the survey form, it should be "not provided". Other cases are "no smoking history".
Detailed classification of smoking history	When "smoking" is checked among the items for smoking history in the survey form, or when any descriptions are made in the smoking period of "smoking", they should be classified as "smoking". When "in the past" is checked or any descriptions are made in the smoking period "in the past" in patients who are not classified as "smoking", the case should be classified as "only in the past (not smoking now)". When "with smoking" is checked but nothing is checked in the detailed classification, or when "unknown" is checked, they should be "unknown".
Patients with dosing deviation of Humira	Patients other than those who satisfied [1] to [4] of "Administration status (dosage and administration)"
Presence/absence of self-administration	When "Self-administration" in the "Administration status of Humira" column is checked at least once, the case should be classified as "with" self-administration. Others are "without" self-administration.

Data name	Derivation and calculation methods
	When both “administration by physician” and “self-administration” are checked, the case should be “with self-administration”.
Presence/absence of self-administration error	When “with” self-administration error is checked in the survey form, it should be classified as “with” the error. When “without” is checked, it should be “without” the error. When some details are provided along with the onset date in the self-administration error column irrespective of a check on “with”/”without”, it should be regarded as “with” the error. If nothing is described there, it should be “unknown/not provided”.
Sex	It should be identified based on the sex in the patient’s information of the survey form. When multiple items are checked or data without a description are included, the case should be classified as “unknown/not provided”.
Pregnancy/nursing	It should be identified based on pregnancy/nursing in the patient’s information of the survey form. When multiple items are checked or data without a description are included even if the sex has been selected as “woman”, the case should be classified as “unknown/not provided”. If the sex is not “woman” even though a description has been made for this item, it is excluded from the calculation.
Race	It should be identified based on the race in the registration form. When multiple items are checked or data without a description are included, the case should be classified as “unknown/not provided”.
Age	It should be identified based on the year and month of the patient’s birth or the first administration date of Humira in the survey form. For the date of birth, the first day should be imputed to identify it, using the following SAS code. floor((intck('month', date of birth, the first administration date of Humira) - (day(the first administration date of Humira) < day(date of birth)))/12) Of note, if it is impossible to identify the date of birth or the first administration date of Humira due to an incomplete or unknown date, select the age provided in the survey form. If it cannot be identified based on the date of birth or the age is not provided, it is defined as “unknown/not provided”.
Pediatrics	Patients aged <15 years
The elderly	Patients aged ≥65 years

Data name	Derivation and calculation methods
Body weight	It should be identified based on the body weight in the patient's information of the survey form. When "unknown" is checked or data without a description are included, it should be "unknown/not provided".
Body height	It should be identified based on the height in the patient's information of the survey form. When "unknown" is checked or data without a description are included, it should be "unknown/not provided".
BMI	Body weight (kg) / (Body height (cm)/100)^2
Duration of illness (in years)	"For XX years and XX months" should be converted into the figure in 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.
Indication	If both "colitis ulcerative" and "others" are checked for indication in the survey form, it should be calculated as "colitis ulcerative".
Site of disease	It should be identified based on "site of disease of colitis ulcerative" in the survey form. Select "unknown/not provided" for undescribed data".
HBs antigen test	Conducted: When "HBs antigen test" in the survey form was conducted (If "conducted" was not checked but the test results were provided, it should be regarded as "conducted") Not conducted: When "HBs antigen test" in the survey form was not conducted Unknown/not provided: other than the above
HBs antibody test	Conducted: When "HBs antibody test" in the survey form was conducted (If "conducted" was not checked but the test results were provided, it should be regarded as "conducted") Not conducted: When "HBs antibody test" in the survey form was not conducted Unknown/not provided: other than the above
HBc antibody test	Conducted: When "HBc antibody test" in the survey form was conducted (If "conducted" was not checked but the test results were provided, it should be regarded as "conducted")

Data name	Derivation and calculation methods
	Not conducted: When “HBc antibody test” in the survey form was not conducted Unknown/not provided: other than the above
HBV-DNA quantification assay	Conducted: When “HBV-DNA quantification assay” in the survey form was conducted (If “conducted” was not checked but the assay results were provided, it should be regarded as “conducted”) Not conducted: Not conducted: When “HBV-DNA quantification assay” in the survey form was not conducted Unknown/not provided: other than the above
Tuberculin test or IGRA	Conducted: When either of “Tuberculin test” or “IGRA” was conducted (If “conducted” was not checked but the results were provided, it should be regarded as “conducted”) Not conducted: When neither “Tuberculin test” nor “IGRA” was conducted Unknown/not provided: other than the above
Chest X ray test	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 should have a record in which the chest X ray test was conducted between -90 and 1. Of note, the data in the survey form shall be used.
Chest CT test	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 test should have a record in which the CT test was conducted between -90 and 1. Of note, the data in the survey form shall be used.
Other imaging	When the first administration date of Humira is 1 and a day before the first administration date is -1, the patients who underwent any other imaging should have a record in which the imaging was conducted between -90 and 1. Of note, the data in the survey form shall be used.
Chest X ray or CT test	Conducted: When either “chest X ray” or “CT test” in the survey form was conducted (If “conducted” was not checked but the test results were provided, it should be regarded as “conducted”) Not conducted: other than the above
Presence/absence of prior medications	The drug names described in “prior-medication history for colitis ulcerative” in the survey form should be regarded as the prior

Data name	Derivation and calculation methods
	medications. Note that when a drug code is null, it is not regarded as a prior medication. When prior-medication data are contained in the survey form, it should be classified as “with prior medication”. When there is no description of “presence/absence of prior medications” in the survey form or the assessment is impossible, it should be classified as “unknown/not provided”, and other cases are “without prior medications”.
Presence/absence of prior medication (aminosalicylic acid drug)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if an aminosalicylic acid drug in the survey form is checked, regard the case as “with aminosalicylic acid”. Others are “without aminosalicylic acid”.
Presence/absence of prior medication (corticosteroids)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if corticosteroids in the survey form is checked, regard the case as “with corticosteroids”. Others are “without corticosteroids”.
Presence/absence of prior medication (azathioprine)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if azathioprine in the survey form is checked, regard the case as “with azathioprine”. Others are “without azathioprine”.
Presence/absence of prior medication (6-mercaptopurine)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if 6-mercaptopurine in the survey form is checked, regard the case as “with 6-mercaptopurine”. Others are “without 6-mercaptopurine”.
Presence/absence of prior medication (azathioprin & 6-mercaptopurine)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if azathioprin and 6-mercaptopurine in the survey form are checked, regard the case as “with azathioprin & 6-mercaptopurine”. Others are “without azathioprin & 6-mercaptopurine”.
Presence/absence of prior medication (tacrolimus & ciclosporin)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if tacrolimus & ciclosporin in the survey form is checked, regard the case as “with tacrolimus & ciclosporin”. Others are “without tacrolimus & ciclosporin”.
Presence/absence of	Refer to “171218 drug list_UC”. If prior-medication data of the

Data name	Derivation and calculation methods
prior medication (antibiotics)	applicable drug code are provided in the survey form, or if antibiotics in the survey form is checked, regard the case as “with antibiotics”. Others are “without antibiotics”.
Presence/absence of prior medication (others)	When any items other than biological products in the survey form are checked, and when prior medication data on the drug code applicable to the drug other than aminosalicylic acid drug, corticosteroids, azathioprine, 6-mercaptopurine, tacrolimus, ciclosporin and antibiotics are included in reference to “171218 drug list_UC”, regard it as “with others”. Other cases are “without others”.
Presence/absence of prior medication (Infliximab)	Refer to “171218 drug list_UC”. If prior-medication data of the applicable drug code are provided in the survey form, or if Infliximab in the survey form is checked, regard the case as “with Infliximab”. Others are “without Infliximab”.
Presence/absence of prior medication (other biological products)	When ‘biological products’ is checked in the survey form, and when prior-medication data of the drug codes other than Infliximab are provided in the survey form in reference to “171218 drug list_UC”, regard the case as “with other biological products”. Others are “without other biological products”.
Presence/absence of treatment history with biological products	The cases with either “with prior medication (Infliximab)” or “with prior medication (other biological products)” are regarded as “with a treatment history with biological products”. Others are “without a treatment history with biological products”. As for presence/absence of the history by ‘detailed classification “with” biological products’, if the applicable data among “Infliximab” and “other biological products” are contained, the case is regarded as “with” the history. Others are “without” the history.
Presence/absence of prior treatment	When the description is made in “Prior treatment for colitis ulcerative (including surgery)” of the survey form, regard it as a prior treatment. When prior-treatment data are contained in the survey form, it should be classified as “with prior treatment”. When there is no description of “presence/absence of prior treatment” in the survey form or the assessment is impossible, it should be classified as “unknown/not provided”, and other cases are “without prior treatment”.
Presence/absence of prior treatment (surgery)	Surgery should be selected if the checkbox of prior treatment (surgery) in “prior treatment for colitis ulcerative (including surgery)” is checked and if any prior treatment considered as surgery

Data name	Derivation and calculation methods
	is included in “[Humira UC] Conversion data provided for analysis”. When the data applicable to surgery are contained, regard it as “with surgery”. Others are “without surgery”.
Presence/absence of prior treatment (leukocytapheresis)	If “leukocytapheresis” in “prior treatment (including surgery) for colitis ulcerative” is checked and it is not applicable to with prior treatment (surgery) in the survey form, it shall be classified into “with leukocytapheresis”. Other cases are “without leukocytapheresis”.
Presence/absence of prior treatment (enteral nutrition therapy)	If “enteral nutrition therapy” in “prior treatment (including surgery) for colitis ulcerative” is checked and it is not applicable to with prior treatment (surgery) in the survey form, it shall be classified into “with enteral nutrition therapy”. Other cases are “without enteral nutrition therapy”.
Presence/absence of prior treatment (intravenous nutrition therapy)	If “intravenous nutrition therapy” in “prior treatment (including surgery) for colitis ulcerative” is checked and it is not applicable to with prior treatment (surgery) in the survey form, it shall be classified into “with intravenous nutrition therapy”. Other cases are “without intravenous nutrition therapy”.
Presence/absence of prior treatment (other therapy)	If “other therapy” in “prior treatment (including surgery) for colitis ulcerative” is checked and it is not applicable to with prior treatment (surgery) in the survey form, it shall be classified into “with other therapy”. Other cases are “without other therapy”.
Presence/absence of concomitant medication	Concomitant medications should the data satisfying the following rules: Note that when a drug code is null, it is not regarded as a concomitant medication. When concomitant-medication data are contained in the survey form, it should be classified as “with concomitant medications”. When there is no description of “presence/absence of prior/concomitant medications” in the survey form or the assessment is impossible, it should be classified as “unknown/not provided”, and other cases are “without concomitant medications”. ◆ Data with drug names in “the administration status of prior/concomitant medications for colitis ulcerative”, “the administration status of other concomitant medication” of the survey form.

Data name	Derivation and calculation methods
	・ 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 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 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. ◆ Data with drug names in “prior treatment history for colitis ulcerative” of the survey form ・ When the year and month are described for the first administration date of the prior medication, impute “1” for the “date”. ・ When the year is described for the final administration date of the prior medication, impute “1” each for the month and the date. ・ If the final administration date of the prior medication ≥ the first administration date of Humira, regard it as a concomitant medication. If the above imputing methods do not help add the date, the final administration date of the prior medication shall be unknown and the case should not be regarded as a concomitant medication.

Data name	Derivation and calculation methods
	◆ Data with a drug name in "administration status of anti-tuberculosis drug" of the survey form ・ When the year and month are described for the first administration date of anti-tuberculosis drug, impute "1" for the "date". ・ When the year is described for the first administration date of anti-tuberculosis drug, impute "1" each for the "month" and "date". ・ When the year and month are described for the final administration date of anti-tuberculosis drug, impute the month's final date for the date. ・ When the year is described for the final administration date of anti-tuberculosis drug, impute "12" for the month and "31" for the date. ・ When the final administration of anti-tuberculosis drug < the first administration date of Humira, and/or when the final administration date of Humira < the first administration date of anti-tuberculosis drug, 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 anti-tuberculosis drug 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 of figure only is provided.)
Presence/absence of concomitant medication (aminosalicylic acid drug)	Refer to "171218 drug list_UC". If concomitant-medication data of the applicable drug code are provided in the survey form, regard the case as "with aminosalicylic acid". Others are "without aminosalicylic acid".
Presence/absence of concomitant medication (corticosteroids)	Refer to "171218 drug list_UC". If concomitant-medication data of the applicable drug code are provided in the survey form, regard the case as "with corticosteroids". Others are "without corticosteroids".
Presence/absence of	Refer to "171218 drug list_UC". If concomitant-medication data of

Data name	Derivation and calculation methods
concomitant medication (azathioprine)	the applicable drug code are provided in the survey form, regard the case as “with azathioprine”. Others are “without azathioprine”.
Presence/absence of concomitant medication (6-mercaptopurine)	Refer to “171218 drug list_UC”. If concomitant-medication data of the applicable drug code are provided in the survey form, regard the case as “with 6-mercaptopurine”. Others are “without 6-mercaptopurine”.
Presence/absence of concomitant medication (azathioprine & 6-mercaptopurine)	Refer to “171218 drug list_UC”. If concomitant-medication data of the applicable drug code are provided in the survey form, regard the case as “with azathioprine & 6-mercaptopurine”. Others are “without azathioprine & 6-mercaptopurine”.
Presence/absence of concomitant medication (tacrolimus & ciclosporin)	Refer to “171218 drug list_UC”. If concomitant-medication data of the applicable drug code are provided in the survey form, regard the case as “with tacrolimus & ciclosporin”. Others are “without tacrolimus & ciclosporin”.
Presence/absence of concomitant medication (antibiotics)	Refer to “171218 drug list_UC”. If concomitant-medication data of the applicable drug code are provided in the survey form, regard the case as “with antibiotics”. Others are “without antibiotics”.
Presence/absence of concomitant medication (others)	When concomitant-medication data on the drug code applicable to the drug other than aminosalicylic acid drug, corticosteroids, azathioprine, 6-mercaptopurine, tacrolimus, ciclosporin and antibiotics are included in reference to “171218 drug list_UC”, regard it as “with others”. Other cases are “without others”.
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 concomitant therapy	It should be described in “non-medicinal treatment/concomitant therapy (including surgery) for colitis ulcerative” of the survey form. The data from the first administration date to the final administration date of Humira will be calculated. Such data are also subject to calculation even if the first/final administration dates of concomitant treatment are not unknown. (Only when the days are not overlapped with the administration

Data name	Derivation and calculation methods
	period of Humira, they shall be excluded from the calculation.) When concomitant-therapy data are contained in the survey form, it should be classified as “with concomitant therapy”. When “presence/absence of prior/concomitant medications” is not provided in the survey form or the assessment is impossible, it should be classified as “unknown/not provided”, and other cases are “without concomitant therapy”.
Presence/absence of concomitant therapy (surgery)	Surgery should be selected when the ‘surgery’ checkbox of non-medicinal treatment/concomitant therapy name is checked in “non-medicinal treatment/concomitant therapy for colitis ulcerative (including surgery)” and when any concomitant therapy considered as surgery is included in “[Humira UC] Conversion data provided for analysis”. When the data applicable to surgery are contained, regard it as “with surgery”. Others are “without surgery”.
Presence/absence of concomitant therapy (leukocytapheresis)	If “leukocytapheresis” in “non-medicinal treatment/concomitant therapy (including surgery) for colitis ulcerative” is checked and it is not applicable to with concomitant therapy (surgery) in the survey form, it shall be classified into “with leukocytapheresis”. Other cases are “no leukocytapheresis”.
Presence/absence of concomitant therapy (enteral nutrition therapy)	If “enteral nutrition therapy” in “non-medicinal treatment/concomitant therapy (including surgery) for colitis ulcerative” is checked and it is not applicable to with concomitant therapy (surgery) in the survey form, it shall be classified into “with enteral nutrition therapy”. Other cases are “no enteral nutrition therapy”.
Presence/absence of concomitant therapy (intravenous nutrition therapy)	If “intravenous nutrition therapy” in “non-medicinal treatment/concomitant therapy (including surgery) for colitis ulcerative” is checked and it is not applicable to with concomitant therapy (surgery) in the survey form, it shall be classified into “with intravenous nutrition therapy”. Other cases are “no intravenous nutrition therapy”.
Presence/absence of concomitant therapy (other therapy)	If “other therapy” in “non-medicinal treatment/concomitant therapy (including surgery) for colitis ulcerative” is checked and it is not applicable to with concomitant therapy (surgery) in the survey form, it shall be classified into “with other therapy”. Other cases are “no

Data name	Derivation and calculation methods
	other therapy".
Tuberculosis test	Conducted: when both "Tuberculin test or IGRA" and "Chest X ray or CT test" were conducted Not conducted: other than the above
Hepatitis B test	Conducted: when "HBV-DNA quantification assay" in the survey form was conducted, or when the results are negative in HBs antigen test, HBs antibody test, and HBc antibody test. Not conducted: other than the above

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 "AE matching results". 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 "AE matching results", 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 events.
Adverse reaction	All events which are not determined as "Not related" based on the company's causality assessment provided in "AE matching results" are regarded as an adverse reaction. With adverse reaction: at least 1 record on adverse reaction(s) exists Without adverse reaction: other than the above.

Data name	Derivation and calculation methods
	Follow the way of counting adverse events to count adverse reactions.
Serious adverse reactions	Based on the seriousness criteria for company assessment which are provided in “AE matching results”, regard the events which have been assessed to be serious as serious adverse reactions. With serious adverse reaction: at least 1 record on serious adverse reaction(s) exists Without serious adverse reaction: other than the above. Follow the way of counting adverse events to count serious adverse reactions.
Outcome	If more than one identical SOC or PT are found in a patient in counting adverse events, adverse reactions, serious adverse events, and serious adverse reactions per outcome, identify the events to be counted with the following priority, using the outcomes for company assessment provided in “AE matching results”. [1] death [2] with sequela [3] not recovered [4] unknown [5] not provided [6] recovering [7] recovered
Death case	At least a piece of data on “death” is found as the outcome of the adverse events during the safety analysis period.
Days from the first administration date of Humira to the adverse-event onset date	Use the onset date for company assessment provided in “AE matching results”. 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	Use the onset date and the outcome confirmation date (recovered or recovering)for company assessment provided in “AE matching results”. 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

Data name	Derivation and calculation methods
recovering)	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.
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

Data name	Derivation and calculation methods
General improvement rate	Use what has been provided in “general improvement rate (primary physician’s assessment” of the survey form.
Mayo score	Partial Mayo score + endoscopic finding score * Only the survey forms with all the scores assessed are calculated (if any unassessed scores are included, they are excluded from calculation)
Remission of Mayo score	It should be calculated as 1 or less if the Mayo score is 2 or below and a sub-score.
Partial Mayo score	Stool frequency score, rectal bleeding score and physician’s global assessment * Only the survey forms with all the scores assessed are calculated (if any unassessed scores are included, they are excluded from calculation)
Remission of partial Mayo score	It should be calculated as 1 or less if the partial Mayo score is 2 or below and a sub-score.
Improvement of partial Mayo score (responder)	Partial Mayo score at every assessment decreases by 2 points or more and by 30% or more in comparison to the partial Mayo score when administration was started. In addition, at least one of the following conditions shall be met. ・Rectal bleeding score has been decreased by at least 1 point since the administration was started. ・Rectal bleeding score is ≤1.
Endoscopy results	Use what has been provided in “endoscopic findings” of the survey form.

11. How to stratify data

Data	How to stratify
Dosage and administration	160mg→80mg→40mg once every two weeks and no changes thereafter, other
Dose period	The first administration to <Week 4 of administration, (1-28 days) ≥Week 4 of administration and <Week 8 of administration (29-56 days) ≥Week 8 of administration and <Week 24 of administration (57-168 days) ≥Week 24 of administration and <Week 48 of administration (169-336 days) ≥Week 48 of administration and ≤Week 52 of administration (337-365 days) Unknown * when the first administration is counted as 1.
Dosing frequency	≥1 and ≤4, ≥5 and ≤12, ≥13 and ≤24, ≥25
Total dose	≥40mg and ≤500mg, ≥501mg and ≤1000mg, ≥1001mg
Reason for discontinuation	Development of adverse event, lack of effectiveness, patient's wish, no visit, others, multiple answers are acceptable
Reason for discontinuation, other reasons	Treatment/surgery, pregnancy, concern about the onset of adverse events, the condition improved, the condition worsened Poor adherence, for study
Sex	Man, women, unknown/not provided
Pregnancy/nursing	Not pregnant/nursing, pregnant, nursing, unknown/not provided
Race	Japanese, other Asians, others, 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 years)	<2, ≥2 and <10, ≥10, unknown/not provided
Indication (registration form)	Colitis ulcerative, others, not provided

Data	How to stratify
Allergy history	Without the history, with the history, unknown/not provided
Smoking history	Without the history, with the history, unknown/not provided
Detailed classification of smoking history	Smoking, only in the past (not smoking now), unknown
Tuberculosis test	Not conducted, conducted
Hepatitis B test	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 colitis ulcerative	Without the history, with the history, unknown/not provided
Details classification of prior medications for colitis ulcerative	Infliximab, other biological products, aminosalicylic acid products, corticosteroid, azathioprine & 6-mercaptopurine, tacrolimus & ciclosporin, antibiotics, prior medication: others
Prior treatment for colitis ulcerative	Without the history, with the history, unknown/not provided
Details classification of prior treatment for colitis ulcerative	Leukocytapheresis, surgery, enteral nutrition therapy, intravenous nutrition therapy, others
Treatment history with biological products	Without the history, with the history, unknown/not provided
Detailed classification of “with” biological products	Infliximab, other biological products Reason for discontinuation: lack of effectiveness Reason for discontinuation: adverse events Reason for discontinuation: others Reason for discontinuation: unknown/not provided
Concomitant medications for colitis ulcerative	Without the history, with the history, unknown/not provided
Details classification of	Aminosalicylic acid products, corticosteroid, azathioprine &

Data	How to stratify
concomitant medications for colitis ulcerative	6-mercaptopurine, tacrolimus & ciclosporin, antibiotics, others
Concomitant therapy for colitis ulcerative	Without the history, with the history, unknown/not provided
Details classification of concomitant therapy for colitis ulcerative	Leukocytapheresis, surgery, enteral nutrition therapy, intravenous nutrition therapy, others
Site of disease	Rectum, colon, unknown/not provided
Details classification of a site of disease "colon"	Sigmoid, descending, transverse, ascending
Site of disease by type	Rectal only (no colon), including any of transverse or ascending site, others, unknown/not provided
Self administration	Without the history, with the history, unknown/not provided
Self-administration error	Without the history, with the history, unknown/not provided
General improvement rate	Effective or better, ineffective
Detailed classification of effective or better of general improvement rate	Markedly effective, effective
Partial Mayo score	≥0 and <3, ≥3 and <6, ≥6 and <9, unknown/not provided
CRP	<0.3mg/dL, ≥0.3mg/dL and <1mg/dL, ≥1mg/dL, unknown/not provided
Endoscopy results	normal or remission mucosa, mild, moderate, severe

12. Handling of data for test/assessment periods

12.1. 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
≥Week 4 of administration and <Week 8 of administration	29~56
≥Week 8 of administration and <Week 24 of administration	57~168
≥Week 24 of administration and <Week 48 of administration	169~336
≥Week 48 of administration and ≤Week 52 of administration	337~365

12.2. 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
≥Week 4 of administration and <Week 8 of administration	29-56
≥Week 8 of administration and <Week 24 of administration	57-168
≥Week 24 of administration and <Week 48 of administration	169-336
≥Week 48 of administration and ≤Week 52 of administration	337-365
> Week 52 of administration	366-

12.3. Assessment period for Mayo score

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	-14 ~ 1 (scheduled date: 1)
Week 24 of administration	155 ~ 183 (scheduled date: 169)
Week 52 of administration	337 ~ 393 (scheduled date: 365)
At discontinuation	The final administration date of Humira + 14 (scheduled date: the final administration date of Humira)
At final assessment	Data for the final assessment period among the assessment applicable to the Time Allowance of each assessment period.

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

12.4. Assessment period for partial Mayo score

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	-14 ~ 1 (scheduled date: 1)
Week 4 of administration	15 to 42 (scheduled date: 29)
Week 8 of administration	43 to 70 (scheduled date: 57)
Week 16 of administration	98 to 126 (scheduled date: 112)
Week 24 of administration	155 ~ 183 (scheduled date: 169)
Week 52 of administration	337 ~ 393 (scheduled date: 365)
At discontinuation	The final administration date of Humira + 14 (scheduled date: the final administration date of Humira)
At final assessment	Data for the final assessment period among the assessment applicable to the Time Allowance of each assessment period.

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

12.5. Assessment period for general improvement rate

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

Assessment period	Time Allowance(Day)
At Week 52 of administration or when the administration is discontinued	・Discontinued patients 1 to the final administration date of Humira + 14 (scheduled date: the final administration date of Humira) ・Other than discontinued patients 1 to 393 (scheduled date: 365)

12.6. Assessment period for CRP

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	-14 ~ 1 (scheduled date: 1)
Week 4 of administration	15 to 42 (scheduled date: 29)
Week 8 of administration	43 to 70 (scheduled date: 57)
Week 24 of administration	155 ~ 183 (scheduled date: 169)
Week 52 of administration	337 ~ 393 (scheduled date: 365)
At discontinuation	The final administration date of Humira + 14 (scheduled date: the final administration date of Humira)
At final assessment	Data for the final assessment period among the assessment applicable to the Time Allowance of each assessment period.

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

12.7. 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
Week 8 of administration	57
Week 16 of administration	113
Week 24 of administration	169
Week 52 of administration	365

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

13.1. General

"1.1 Case structure chart"

Patients for analysis: registered patients

Analysis objective: to indicate changes in the number of patients

Analysis items: number of registered sites, 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, 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

Note: If the reason for exclusion is null for an item, the item itself will not be displayed.

"1.2 The number of sites for survey and the number of patients surveyed"

Patients for analysis: patients whose survey form was locked

Analysis objective: to show the number of patients per site

Analysis items: number of sites with patients whose survey form has been locked, number of patients whose survey form was locked, the mean number of patients per site

To show the maximal, minimal number of patients

"1.3 A list of the patients excluded from the safety analysis group and the patients excluded from the effectiveness analysis group (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 not 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 the reason for exclusion in each analysis group regarding all the patients in the analysis group.

Analysis items: patients whose survey form was yet to be locked, patients excluded from the safety analysis group, the breakdown of reasons for exclusion from the safety analysis group, patients

excluded from the effectiveness analysis group, the breakdown of reasons for exclusion from the effectiveness analysis group

Note: After all patients' data are displayed, display "1" at the applicable column. If not applicable, leave the column blank. For "Data credibility not confirmed" in the "reason for exclusion from the safety analysis", display the breakdown. If more than one category for the 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), general improvement rate, 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, HBs antibody, HBc antibody, HBV-DNA quantitative assay, hepatitis B test), with/without administration of anti-hepatitis B virus agent, tuberculosis (Tuberculin test, QuantiFERON test, T-spot test, chest X ray test, Thoracic CT test, other imaging, tuberculosis test), search flags (patients in the safety analysis group, patients in the effectiveness analysis group, discontinued patients, death cases, pediatrics, the elderly, pregnant, nursing, liver disorder, renal disorder, patients with hepatitis B viral infection, patients with an infection, patients with cytomegalovirus infection, patients with tuberculosis, patients with malignant tumour, patients with administration site reaction, patients with autoimmune disease, patients with pancytopenia, patients with demyelinating disease, patients with cardiac failure congestive, patients with interstitial pneumonia, patients deviated from the administration of Humira, patients with self-administration error, patients with AAA measured, contraindication)

Note: Follow "12.5 Assessment period for general improvement rate" to display the general improvement rate.

Also, display "markedly effective", "effective", "ineffective" and "effectiveness is not assessable".

Use 1 (applicable) or 0 (not applicable) to show adverse events which occurred not in the safety analysis period and search flags.

"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 to the onset, seriousness, causality, outcome, outcome confirmation date, days to the outcome confirmation, complication, patients in the safety analysis group, reason for exclusion from the safety analysis group, patients in the effectiveness analysis group, patients with adverse events not in the safety analysis period, discontinued patients, death cases, pediatrics, the elderly, pregnant, nursing, liver disorder, renal disorder, patients with hepatitis B viral infection, patients with an infection, patients with cytomegalovirus infection, patients with tuberculosis, patients with malignant tumour, patients with administration site reaction, patients with autoimmune disease, patients with pancytopenia, patients with demyelinating disease, patients with cardiac failure congestive, patients with interstitial pneumonia, patients deviated from the administration of Humira, patients with self-administration error, patients with AAA measured, contraindication

Note: The definition of analysis item is the same in "1.4 A list of patients".

Use PT for complications. If a patient has more than one complication, 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 item: Follow "1.4.1 A list of adverse events".

"1.4.3 A list of prior/concomitant medications in patients with an CMV infection"

Patients for analysis: patients whose survey form was locked

Analysis objective: to show a list of adverse events in patients with an CMV infection by using analysis data.

Analysis item: the patients with at least one PT code in "180111 patients with an CMV infection" among adverse events which occurred in the safety analysis period".

Display the drug name and drug code of prior/concomitant medications for each patient. If more than one drug code exists in a patient, display them in a comma-delimited manner.

"1.4.4 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,

discontinued/not discontinued, reason for discontinuation, adverse event (SOC code, System Organ Class, PT code, name of disease (MedDRA PT), onset date, seriousness, causality, outcome, outcome confirmation date), general improvement rate, Administration status of Humira (the first and the final administration dates), complication (PT code, name of disease (MedDRA PT), Medical history (PT code, name of disease (MedDRA PT)), site of disease of colitis ulcerative (rectum, colon, sigmoid, descending, transverse, ascending), Mayo score (at the first administration, Week 24 and Week 52 of administration), Partial Mayo score (at the first administration, Week 8, Week 24, and Week 52 of administration), Search flag (prior medication (Infliximab, other biological products, aminosalicylic acid drug, corticosteroids, azathioprine & 6-mercaptopurine, tacrolimus & ciclosporin, antibiotics))

"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: calculate the number of patients in the analysis groups as well as the percentage to the number of patients and the number of those in the analysis groups per segment defined in "administration status (dosage and administration)" of "10.1 General".

"1.5.1 other dosage and administration (a list)"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show a list of reasons for change in dose/dosing frequency in patients classified into the dose and administration "others".

Analysis items: Select the patients who are categorized in "others" defined in "administration status (dose and administration)" of "10.1 General", and display the case number and the reason for the change in dose/dosing frequency.

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

Note: Follow the definition in "the reason for the change in dose/dosing frequency" of "10.1 General" for the reason for the change in dose/dosing frequency.

"1.6 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" as well as the percentage to the number of patients in the analysis groups regarding dosing frequency and the total dose. In addition, calculate summary statistics for each measurement.

"1.6.1 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" as well as the number of patients in the analysis groups. Then, calculate the number of patients per segment which contains the administrations date in each patient and the percentage to the patients in the analysis group in the Time Allowance defined in "12.1 Assessment period for administration status of Humira" In addition, calculate summary statistics for the number of days for administration.

"1.6.2 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: At Risk, number of discontinued patients, continuation rate (the percentage to the number of discontinued patients for At Risk), 95% of continuation rate

Calculate the confidence interval by assessment period. In addition, generate the Kaplan-Meier curve for the continuation rate.

Note: Follow "12.7 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 + 364 in patients who are still registered at Week 52.

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 it per item.

“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 segment of “reason for discontinuation, other reason”. Display the segments in descending order of number of patients.

“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. In addition, calculate summary statistics for each measurement.

Sex, pregnancy/nursing, race, 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 test, complication, detailed classification of complications, complication/others, medical history, detailed classification of medical history, prior medication for colitis ulcerative, detailed classification of prior medication for colitis ulcerative, prior treatment for colitis ulcerative, detailed classification of prior treatment for colitis ulcerative, treatment history with biological product, detailed classification of “with” biological product, concomitant medication for colitis ulcerative, detailed classification of concomitant medication for colitis ulcerative, concomitant treatment for colitis ulcerative, detailed classification of concomitant treatment for colitis ulcerative site of disease, the detailed classification of the disease site “colon”, site of disease by type, partial Mayo score, CRP

Note: For the discontinuation reasons for the detailed classification of pregnant/nursing or ‘using’ biological products”, calculate the percentage to the aggregation item right above the item. For other items, calculate the percentage to the number of target patients.

Overlapped aggregation may occur in the detailed classification of complications and complication of other classification, detailed classification of medical history, detailed classification of prior medications for colitis ulcerative, detailed classification of prior treatment for colitis ulcerative, detailed classification of ‘using’ biological products”, detailed classification of concomitant medications for colitis ulcerative, detailed classification of concomitant treatment for colitis ulcerative, and the detailed classification of site of disease for colitis ulcerative and the site of

disease “colon”.

“1.13 Incidence of self-administration error”

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the distribution status for presence/absence of self-administration and the detailed classification 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.

In addition, calculate the number of patients per “self-administration error” and the percentage to the patients ‘with’ self-administration.

“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, general improvement rate

Note: Show “continued” for patients who are still registered in the survey.

Obtain information on serum anti-adalimumab antibody from “UC Survey AAA Measurement (periodic safety report).

Follow “12.5 Assessment period for general improvement rate” for the general improvement rate.

13.2. Safety

“2.1 A list of onset status of adverse reactions/infections (Attachment Form 2) ”

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the onset status of adverse reactions

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 sites surveyed, 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: the classification of the period is as follows:
The 6th periodic safety report: at approval, from June 14, 2013 to December 31, 2015, from January 1, 2016 to December 31, 2016, cumulative, total
Re-examination: at approval, June 14, 2013 to December 31, 2015, January 1, 2016 to December 31, 2016, January 1, 2017 to May 15, 2017, cumulative, total.
Final report: at approval, cumulative, total

Put * before the PT of unexpected events from "Precautions".

"2.1.1 A list of the onset status of adverse reactions/infections (patients not in the safety analysis)"

Patients for analysis: patients excluded from the safety analysis group
Analysis objective: to show the onset status of adverse reactions, etc. in patients not in the safety analysis group.
Analysis item: aggregate the following items 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 sites surveyed, 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).

"2.1.2 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, etc. which occurred not in the follow-up period.
Analysis item: aggregate the following items for 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 sites surveyed, 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).

"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: see “2.1 A list of the onset status of adverse reactions/infections (Attachment Form 2)” on how to separate the period.
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 “[Humira UC]DCF code list_Company A” and “[Humira UC]DCF code list_Company E”.

(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 classification”.

(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 PT code and PT from the indication of Humira described in the survey form. If the indication is ‘other’, obtain the indication from “[Humira UC] indication, other detailed coding”.

(10) Severity prior to administration
Four stages of “physician’s global assessment” at first administration in “Effectiveness assessment (partial Mayo-score)” of the survey form: remission phase, mild, moderate and severe
Select the data dated before the first administration date. If the date is behind the first administration date, select “no assessment”. If the date is not provided or unknown, select

“unknown”.

(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 day/volume)

The daily maximum dose Select the largest number in “administration status (dose and administration) defined in “10.1 General” per patient.

(14) The mean dose (a day/volume)

The mean daily 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 them with sequence with the priority of concomitant medications for colitis ulcerative per patient, and choose the top concomitant medication. 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 drug codes arranged as mentioned above. If more than 1 identical drug code is found in a patient, count it as 1. Describe “0” for the case with no concomitant medications.

(19) Effectiveness level

Display the general improvement rate calculated in accordance with “12.5 Assessment period of general improvement rate”. Of note, as for the patients with no general improvement rate calculated in accordance with 12.5, if there is a description on the assessment in the survey form, use the description. If not, display “not described”. If it is not assessable, display “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 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 "days from the first administration date of Humira to the adverse-event onset date" defined in "10.2 Safety analysis".
- Outcome: identify it as mentioned in "outcome" defined in "10.2 Safety analysis".
- Days to outcome (recovered or recovering): identify the days as mentioned in "days from the first administration date of Humira to the outcome confirmation date (recovered or recovering)" defined in "10.2 Safety analysis".

"2.4.2 A list of the onset status of adverse reactions (identified important risks)"

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the summary statistics of the days to the onset, the number of patients per outcome, and the days to the onset and the days to the outcome (recovered or recovering) regarding the adverse reactions of identified important risks based on "20180115_how to extract risks (RMP)_MedDRA20.1".

Analysis items: calculate the number of cases 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 per type of identified important risks (identified important risks, PT), 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 identified important risks (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, refer to "2.4.1 A list of the onset status of adverse reactions (priority survey items)"

“2.4.3 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 item: handle the items for analysis and definitions as mentioned in “2.4.1 A list of the onset status of adverse reactions (priority survey item)” for adverse events which occurred in the safety analysis period.

“2.4.4 A list of the onset status of adverse events (identified important risks)”

Patients for analysis: patients in the safety analysis group

Analysis objective: to show the summary statistics of the days to the onset, the number of patients per outcome, and the days to the onset and the days to the outcome (recovered or recovering) regarding the adverse events of identified important risks based on “20180115_how to extract risks (RMP)_MedDRA20.1”.

Analysis item: handle the items for analysis and definitions as mentioned in “2.4.2 A list of the onset status of adverse reactions (identified important risks)” for adverse events which occurred in the safety analysis period.

“2.5 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).

“2.5.1 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. type of adverse reactions, etc. (SOC, PT).

Note: Aggregate the initial events 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 "12.2 Assessment period for the onset status of adverse reactions". When calculating the number of patients with the target events, remove unnecessary data per case number and onset period. When calculating the number of SOC, remove unnecessary data per case number, onset period and SOC.

Count the number of patients surveyed by using the date defined below until the assessment period applicable to Time Allowance defined in "12.2 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 + 392 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. type of adverse reactions, etc. (SOC, PT).

Note: Refer to the note of "2.6 Incidence of adverse reactions per onset period (serious)".

"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: the patient background factors are as follows:
Age (year), the elderly, pediatrics, sex, body weight (kg), BMI (kg/m^2), duration of illness (year), complications, complication: hepatic function disorder, complication; renal impairment, 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, allergy history, smoking history, detailed history of smoking history, the administration status of Humira: self-administration, prior medication, prior medication: biological product, prior medication Infliximab, prior medication: other biological product, prior medication: aminosalicylic acid drug, prior medication: corticosteroids, prior medication: azathioprine, prior medication 6-mercaptopurine, prior medication: azathioprine & 6-mercaptopurine, prior medication: tacrolimus & ciclosporin, prior treatment, prior treatment: leukocytapheresis, prior treatment: surgery, prior treatment: enteral nutrition therapy, prior treatment: intravenous nutrition therapy, concomitant medication, concomitant medication: aminosalicylic acid drug, concomitant medication: corticosteroids, concomitant medication: azathioprine, concomitant medication: 6-mercaptopurine, concomitant medication: azathioprine & 6-mercaptopurine, concomitant medication: tacrolimus & ciclosporin, concomitant treatment, concomitant treatment: leukocytapheresis, concomitant treatment: surgery, concomitant treatment: intravenous nutrition therapy, concomitant treatment: enteral nutrition therapy, site of disease by type, partial Mayo score, 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 events, remove unnecessary data per case number and seriousness. When calculating the number of SOC, remove unnecessary 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 show the onset status of adverse reactions in pediatrics and non-pediatrics per outcome.

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 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, etc. and serious adverse reactions, etc.
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.

“2.18 A list of the onset status of adverse reactions with/without treatment history with biological products”.
Patients for analysis: patients in the safety analysis group
Analysis objective: to show the onset status of adverse reactions with/without treatment history with biological products.
Analysis item: aggregate the following items with/without treatment history with biological products 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).

"2.18.1 A list of the onset status with/without treatment history with biological products (patients excluded from the safety analysis group)"

Patients for analysis: patients excluded from the safety analysis group

Analysis objective: to show the onset status of adverse reactions with/without treatment history with biological products.

Analysis item: aggregate the following items with/without treatment history with biological products 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).

"2.19 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: When more than one identical PT is found in a patient, aggregate the event as 1 patient (case) in the following manner:

・Seriousness priority: serious > non-serious

"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 calculate the following items by 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 with adverse reactions, incidence of the reactions, number of adverse reactions and type of adverse reactions (SOC, PT). In addition, show the number of cases per days to outcome (recovered or recovering), number of patients per outcome, summary statistics of days to the onset per type of adverse reactions (PT).

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 “days from the first administration date of Humira to the adverse-event onset date” defined in “10.2 Safety analysis”.
- Outcome: identify it as mentioned in “outcome” defined in “10.2 Safety analysis”.
- Days to outcome (recovered or recovering): identify the days as mentioned in “days from the first administration date of Humira to the outcome confirmation date (recovered or recovering)” defined in “10.2 Safety analysis”.

13.3. Effectiveness

“3.1.1 Changes in Mayo score (Observed Case)”

Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show Mayo score and the changes in Mayo score per assessment period.
Analysis item: calculate the number of patients in the analysis groups.
Calculate the number of target patients, the mean and standard deviation of Mayo score, the mean and standard deviation of changes in Mayo score for each assessment period, and conduct a paired-t test which compares the values at the initial administration.

Note: Follow “12.3 Assessment period for Mayo score” for Time Allowance of assessment period.
The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.
Multiplicity in the test will be adjusted by the Bonferroni method.

“3.1.2 Changes in the remission rate at each point of Mayo score (Observed Case)”

Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show the remission rate of Mayo score per assessment period.
Analysis item: calculate the number of patients in the analysis groups.
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.
In addition, prepare a line plot to describe the percentage to the target patients among the patients who achieved a remission per assessment period.
X-axis: assessment period (in week)
Y-axis: percentage (%)

Note: Follow “12.3 Assessment period for Mayo score” for Time Allowance of assessment period.

The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.
For the confidence interval, use the Clopper-Pearson's confidence interval.
Refer to "10.3 Effectiveness analysis" for the calculation method and remission rate.

"3.1.4 Changes in partial Mayo score (Observed Case)"
Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show partial Mayo score and the changes in partial Mayo score per assessment period.
Analysis item: calculate the number of patients in the analysis groups.
Calculate the number of target patients, the mean and standard deviation of partial Mayo score, the mean and standard deviation of changes in partial Mayo score for each assessment period, and conduct a paired-t test which compares the values at the initial administration.
In addition, calculate the mean of the mean days to the final assessment and the standard deviation.

Note: Follow "12.4 Assessment period for partial Mayo score" for Time Allowance of assessment period.
The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.
Multiplicity in the test will be adjusted by the Bonferroni method.

"3.1.5.1 Changes in the remission rate at each point of partial Mayo Score (Observed Case)"
Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show the remission rate of partial Mayo score per assessment period.
Analysis item: calculate the number of patients in the analysis groups.
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.
In addition, prepare a line plot to describe the percentage to the target patients among the patients who achieved a remission per assessment period.
X-axis: assessment period (in week)
Y-axis: remission rate (%)

Note: Follow "12.4 Assessment period for partial Mayo score" for Time Allowance of assessment period.
The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.

For the confidence interval, use the Clopper-Pearson's confidence interval.
Refer to "10.3 Effectiveness analysis" for the calculation method and remission rate.

"3.1.5.2 Changes in the remission rate (NRI) at each point of partial Mayo Score"

Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show the remission rate of partial Mayo score per assessment period.
Analysis item: calculate the number of patients in the analysis groups.
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.
In addition, prepare a line plot to describe the percentage to the target patients among the patients who achieved a remission per assessment period.
X-axis: assessment period (in week)
Y-axis: remission rate (%)

Note: Follow "12.4 Assessment period for partial Mayo score" for Time Allowance of assessment period.
The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.
For the confidence interval, use the Clopper-Pearson's confidence interval.
Refer to "10.3 Effectiveness analysis" for the calculation method and remission rate.
NRI: when it is unknown whether the remission is achieved, impute the data without remission.

"3.1.7.1 Remission rate at Week 52 in patients who achieved a remission at Week 8 of administration based on partial Mayo score"

Patients for analysis: Patients in the effectiveness analysis group (the patients who did not achieve a remission when the administration was started but achieved the remission at Week 8 of administration in partial Mayo score)
Analysis objective: to show the remission rate of partial Mayo score at Week 52 of administration in patients in the analysis group.
Analysis items: calculate the number of target patients, the percentage to the number of patients who achieved a remission at Week 52 of administration and the target patients, and the confidence interval of the remission rate. (calculate them in both Observed Case and NRI patterns)

Note: the patients for analysis should have partial Mayo score at the first administration and Week 8 of administration and achieved a remission at Week 8 of administration except those who had already achieved a remission in partial Mayo score at the first administration.
Follow "12.4 Assessment period for partial Mayo score" for Time Allowance of assessment period.

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

"3.1.7.2 Remission rate at Week 52 in patients who achieved the response as an index of partial Mayo score at Week 8 of administration"

Patients for analysis: Patients in the effectiveness analysis group (the patients who achieved a response at Week 8 of administration in partial Mayo score)

Analysis objective: to show the remission rate of partial Mayo score at Week 52 of administration in patients in the analysis group.

Analysis items: calculate the number of target patients, the percentage to the number of patients who achieved a remission at Week 52 of administration and the target patients, and the confidence interval of the remission rate. (calculate them in both Observed Case and NRI patterns)

Note: the patients for analysis should have partial Mayo score at the first administration and Week 8 of administration and be a responder at Week 8 of administration.

Follow "12.4 Assessment period for partial Mayo score" for Time Allowance of assessment period.

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

Definition of responder: partial Mayo score at every assessment decreases by 2 points or more and by 30% or more. In addition, at least one of the following conditions shall be met.

- Rectal bleeding score has been decreased by at least 1 point since the administration was started.
- Rectal bleeding score is ≤1.

"3.2 General improvement rate"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show the general improvement rate at Week 52 or at discontinuation of administration

Analysis item: calculate the number of patients in the analysis groups.

For the general improvement rate at the final observation which was calculated according to "12.5 Assessment period of general improvement rate", calculate the percentage to the number of patients and the patients in the analysis group per "general improvement rate" and "detailed classification for patients with an effective or better result in general improvement rate" defined in "11 How to stratify data".

"3.4 Aggregation for effectiveness per patient background factor (general improvement rate)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show the effectiveness rate of the general improvement rate at Week 52 or at discontinuation of administration as the primary endpoint and analyze the factors.

Analysis items: calculate the number of patients, the percentage to the number of patients with an effective (markedly effective + effective) in general improvement rate and all patients, the

percentage to the number of patients with an ineffective result in general improvement rate and the number of all patients, the tests for effectiveness (Fisher's exact test for nominal-scale factors and Man-Whitney's u test for ordinal-scale factors) per the following patient background factor.

Note: the patient background factors are as follows:
Age (year), the elderly, pediatrics, sex, body weight (kg), BMI (kg/m^2), duration of illness (year), complications, complication: hepatic function disorder, complication; renal impairment, 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, allergy history, smoking history, detailed history of smoking history, the administration status of Humira: self-administration, prior medication, prior medication: biological product, prior medication Infliximab, prior medication: other biological product, prior medication: aminosalicylic acid drug, prior medication: corticosteroids, prior medication: azathioprine, prior medication 6-mercaptopurine, prior medication: azathioprine & 6-mercaptopurine, prior medication: tacrolimus & ciclosporin, prior treatment, prior treatment: leukocytapheresis, prior treatment: surgery, prior treatment: enteral nutrition therapy, prior treatment: intravenous nutrition therapy, concomitant medication, concomitant medication: aminosalicylic acid drug, concomitant medication: corticosteroids, concomitant medication: azathioprine, concomitant medication: 6-mercaptopurine, concomitant medication: azathioprine & 6-mercaptopurine, concomitant medication: tacrolimus & ciclosporin, concomitant treatment, concomitant treatment: leukocytapheresis, concomitant treatment: surgery, concomitant treatment: intravenous nutrition therapy, concomitant treatment: enteral nutrition therapy, site of disease by type, partial Mayo score, CRP

"3.4.1 Aggregation for effectiveness per patient background factor (partial Mayo score)"
Patients for analysis: patients in the effectiveness analysis group
Analysis objective: to show the remission of partial Mayo score at the final assessment as the primary endpoint per patient background factor and analyze them.
Analysis items: calculate the number of all patients, the percentage to the number of patients who achieved a remission in partial Mayo score and all patients, the number of patients who failed to achieve a remission in partial Mayo score and the percentage to number of all patients, the tests for remission (Fisher's exact test for nominal-scale factors and Man-Whitney's u test for ordinal-scale factors) per the following patient background factor:

Note: Refer to "3.4 Aggregation for effectiveness per patient background factor (general improvement rate)" for patient background factors.

"3.5 Changes in CPR level"

Patients for analysis: patients in the effectiveness analysis group

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

Analysis items: calculate CRP's summary statistics (number of cases, mean, standard deviation, minimum value, 1st quartile value, the median, 3rd quartile value and the maximum value) per assessment period.

Note: Follow "12.6 Assessment period for CRP" for Time Allowance of assessment period.

The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.

"3.6 The status of corticosteroid use and the remission in partial Mayo score in patients who used corticosteroids when administration was started (Observed Case)"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show the status of corticosteroid use and with/without remission in partial Mayo score per assessment period in patients who concomitantly used corticosteroids when administration was started

Analysis items: calculate the number of target patients, the percentage to the number of patients with/without concomitant use of corticosteroids and to the number of target patients, and the percentage to the number of patients who achieved/failed to achieve a remission in partial Mayo score and to the number of target patients.

Note: The target patients to be counted in each assessment period shall receive Humira in each Time Allowance defined in "12.4 Assessment period of partial Mayo score".

The target patients who concomitantly used corticosteroids at each assessment period shall receive corticosteroids at each scheduled date defined in "12.4 Assessment period of partial Mayo score".

Follow "12.4 Assessment period for partial Mayo score" for Time Allowance of the assessment period regarding with/without remission in partial Mayo score.

"3.7 Endoscopy results during administration period"

Patients for analysis: patients in the effectiveness analysis group

Analysis objective: to show endoscopy results at each assessment period.

Analysis item: calculate the number of patients in the analysis groups.

Calculate the number of patients who underwent endoscopy, the number of patients with endoscopy results (normal, remission mucosa, mild, moderate and severe), and the percentage to the patients who underwent endoscopy per assessment period.

Note: Follow “12.3 Assessment period for Mayo score” for Time Allowance of assessment period. The analysis covers only the patients with the assessment applicable to Time Allowance of the first administration and each assessment period.