Humira® for Subcutaneous Injection
Special Investigation (All-Case Surveillance) in Patients with Juvenile Idiopathic arthritis
Study Protocol

Final Analysis
Statistical Analysis Plan
Version 2.0

Date of preparation: March 28, 2018

Approval

Entrustor

Name of company AbbVie GK

Approver Person responsible for management of post-marketing surveillance, etc. Signature

Date of approval MM DD, YYYY

Approver General Manager of Medical Headquarters Signature

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1. History of preparation/revision

Version number	Date of creation/revision	Prepared/Revised by	Reason
1.0	10/23/2017	[redacted]	New document
2.0	03/28/2018		■ Added ● New form "Table 6.1 Frequency of adverse events by severity" ■ Changed ● Table 1.3, Of the breakdown of concomitant drugs, added description on the dose of methotrexate per body surface area ● Table 1.8 Changed the definition of "Other" ● Changed the title Table 2.3, Table 2.5.2, Table 3.5.2, Table 4.1, Table 4.3.4 ● Tests for items that may be aggregated redundantly were no longer required Table 2.5.1, Table 3.1, Table 3.5.2 ● Changed the analysis object from adverse events to adverse reactions Table 2.5.3, Table 2.5.4 ● Deleted annotations Table 3.4.2, Table 3.5.1, Table 3.6.1, Table 3.6.2, Table 4.3, Table 4.3.2 ● Add annotations Table 3.5.3 ● Add items Table 4.2, Table 4.3, Table 4.3.2, Table 4.3.4,

2. Definition of terms and abbreviations

The terms and abbreviations used in this statistical analysis plan are defined as follows.

Terms and abbreviations	Definition
Adverse events	An adverse event refers to any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a drug, whether or not considered related to the drug.
Adverse events during the safety analysis period	Adverse events that occurred during the period up to the start date of Humira treatment + 196 days.
Adverse events outside the safety analysis period	Adverse events that occurred prior to the start date of Humira treatment or after the start date of Humira treatment + 196 days.
Adverse reactions	Of adverse events, events for which causal relationship with Humira cannot be ruled out are defined as adverse reactions.
Adverse reactions during the safety analysis period	Of adverse events during safety analysis period, events for which a causal relationship with Humira cannot be ruled out are defined as adverse reactions during safety analysis period.
Adverse reactions outside the safety analysis period	Of adverse events outside safety analysis period, events for which a causal relationship with Humira cannot be ruled out are defined as adverse reactions outside the safety analysis period.
Basic statistics	Basic statistics include sample size, mean value, standard deviation, minimum value, median value, maximum value, first quartile and third quartile.
MedDRA/J	Medical Dictionary for Regulatory Activities/Japanese edition
SOC	MedDRA/J System Organ Class
PT	MedDRA/J Preferred Term
CDAI	Clinical Disease Activity Index
CRP	C-Reactive Protein
DAS	Disease Activity Score
DMARDs	Disease Modifying Antirheumatic Drugs
EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
SDAI	Simplified Disease Activity Index
VAS	Visual Analog Scale

3. Purpose and rules of this statistical analysis plan

3.1. Purpose of preparation of this statistical analysis plan

The purpose of this statistical analysis plan is to determine the matters related to statistical analysis activities conducted in accordance with the implementation plan of the "Special Drug Use-Results Survey (All-Case Surveillance) on Humira® (generic name: adalimumab [genetical recombination])" (hereafter referred to as "this survey"). This is one of the surveys conducted in compliance with the GPSP Ordinance, and partial or total results of the analysis will serve as data used for reporting of the special drug use-results survey on Humira to authorities and preparation of application materials for reexamination.

4. Survey summary

4.1. Purpose of the survey

This survey is conducted as the special drug use-results survey on Humira® Subcutaneous Injection (generic name: adalimumab [genetical recombination]) for the purpose of understanding the following matters in all patients with juvenile idiopathic arthritis with active articulation treated with Humira.

1) Unknown adverse reactions (clinically significant adverse reactions in particular)
2) Incidence of adverse reactions under actual use conditions
3) Factors considered to have an influence on safety, efficacy, etc.

4.2. Survey plan

The survey objects are all patients with juvenile idiopathic arthritis with active articulation who have a poor response to existing treatment and are to receive Humira. All patients who are to receive Humira will be enrolled after this indication is approved, and aggregation, analysis, and reporting to authorities will be conducted when data from 100 patients have been collected. Even after regulatory reporting, enrollment of patients will be continued until the final evaluation is obtained from regulatory authorities.

4.3. Planned sample size

100 patients

5. Items to be assessed in analysis and examining method

5.1. Safety

5.1.1. Occurrence of adverse reactions

For adverse reactions, see “Data derivation and calculation methods”.

Diagrams will be created to examine the incidence rates of adverse reactions.

5.1.2. Occurrence of serious adverse events

For serious adverse events, see “Data derivation and calculation methods”.

Diagrams will be created to examine the incidence rates of serious adverse events.

5.2. Efficacy

5.2.1. Presence or absence of efficacy

For setting of efficacy, see “Data derivation and calculation methods”.

Diagrams will be created to examine the remission rates.

5.2.2. Trends in efficacy endpoints

For setting of efficacy, see “Data derivation and calculation methods”.

Diagrams will be created to compare the values before the start of treatment, at 4, 8, 12, 16 and 24 weeks of treatment.

6. Implementation status and schedule of analyses

Purpose of analysis	Implementation status (survey unit period, if implemented)	Timing to prepare analysis results
Reexamination replacement	From July 1, 2011 to August 4, 2017	Around December 2017
Final report	From July 1, 2011 to around June 2018	Around June 2018

7. Software/dictrionaries used for analysis

7.1. Statistical analysis and tabulation software

Software and versions used for analyses are shown below.

	Software and version
OS	Microsoft Windows 7 or later
Statistical analysis software	SAS Ver. 9.2 or later
Tabulation software	Microsoft Excel 2007 or later

7.2. Dictionaries used

Dictionaries used for adverse event terms, complication terms and drug names are shown below.

Item	Dictionary name and version	Remarks
Type of adverse event and adverse reaction/infection	ICH Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) *An appropriate version is used for aggregation according to the timing of analysis.	・Adverse events and adverse reactions are classified into System Organ Class (SOC), and appropriate terms should be selected from Preferred Terms (PT). ・When SOC is indicated, it should be in accordance with the order of international agreements. ・When PT is indicated, it should be in accordance with the order

Item	Dictionary name and version	Remarks
		of MedDRA/J code. ・ The version of the MedDRA/J used should be clarified in the margin.
Drug name (concomitant drug)	Prescription drug data file *An appropriate version should be used for aggregation according to the timing of analysis.	・ In principle, 7-digit codes should be used for aggregation of concomitant drugs by drug. ・ In a list of concomitant drugs (including Appended Form 3 for Reexamination), LLT codes should be preferentially used (including Appended Form 3 for Reexamination).

8. Definition of populations used for analysis

Name of population	Definition
Enrolled patients	Patients determined to be eligible for enrollment.
Patients with fixed CRFs	Enrolled patients whose CRF was fixed.
Patients with no CRF collected	Of the enrolled patients, those who have no CRF collected.
Patients excluded from the safety analysis set	Of the patients with fixed CRFs, those who meet any of the following from the list of inclusion of patients. ・ Breach of contract Unsigned facility/clinical department Excess of contracted patients ・ Humira not administered Humira not administered (revealed after collection of a CRF) ・ Humira administered before contract The start date of Humira treatment is outside of the contracted period (survey period) ・ Registration criteria violation/ineligible patient Patients not eligible for the survey (revealed after collection of a CRF) ・ Not confirmed by a doctor Patients whose CRF was signed by a person other than the contracting doctor ・ Unenrolled patient Patients who have not been enrolled but whose CRF has been collected ・ Duplicate patient

Name of population	Definition
	Patients enrolled redundantly within the survey ・ Patients transferred to another hospital Duplicate patient within the survey due to hospital transfer ・ Patients with withdrawn consent Patients who withdrew consent to participation in the survey/study or to the use of data ・ Patients ineligible for safety assessment No record of safety assessment (it is unknown whether or not the patient had any adverse event) ・ Data reliability not confirmed (medical facility closed down or merged, doctor transferred to another facility, confirmation refused by doctor, inconsistent content of CRF) Reliability of the data cannot be confirmed, and an entrustor gave instructions separately
Patients included in the safety analysis set	Patients with fixed CRFs excluding patients excluded from the safety analysis set
Patients excluded from the efficacy analysis set	Of the patients included in the safety analysis set, those who meet any of the following from the list of inclusion of patients. ・ Disease not eligible to the survey Disease defined as not eligible to the survey in the implementation plan ・ Patient ineligible for efficacy assessment DAS 28 (4/ESR) cannot be calculated at any time points after administration of Humira
Patients included in the efficacy analysis set	Patients included in the safety analysis set excluding patients excluded from the efficacy analysis set.

9. General agreements concerning analysis

9.1. Handling of missing data

Missing data will not be complemented, etc. during analysis. However, input data need to be complemented for some items. For the input data requiring complement, the complement methods are defined in the definition of each item in Chapter 10 and subsequent chapters.

9.2. Handling incomplete dates

Missing dates should be treated as “unspecified”. Dates including unknow date, month or year, or dates that cannot be true according to the calendar should be handled as “unknown” without exception.

9.3. Handling of unknown/unspecified

For calculation of percentage, the number of patients with “unknown” or “unspecified” data should be included in denominators. When a test is performed, patients with “unknown” or “undescribed” data should be excluded.

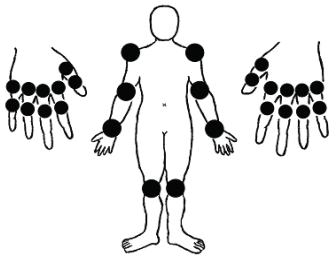
9.4. Handling of adverse events

For subtotals by System Organ Class (SOC), multiple events belonging to the same SOC in a single patient should be counted as 1 event. For subtotals by Preferred Term (PT), multiple events belonging to the same PT in a single patient should be counted as 1 event. SOC should be displayed in the order of international agreements, and PT should be displayed in the order of MedDRA/J code.

9.5. EULAR Response Criteria, Judgment criteria for DAS28

A method to calculate the absolute value of disease activity.

<Evaluation items>



(A) Number joints with tenderness

(a total of 28 joints from left and right shoulders, elbows, hands and knees)

(B) Number of swollen joints

(a total of 28 joints from left and right shoulders, elbows, hands and knees)

(C) Erythrocyte sedimentation rate (ESR) at 1 hour (mm)

(D) Overall disease activity (VAS) (mm)

(Assessment of the degree of overall disease activity of rheumatoid arthritis on a 10-cm line by the patient.)

(E) C-reactive protein (CRP) (mg/dL)

<Calculation formula when an ESR value is used>

$DAS28\text{-}4(ESR) = 0.56\times\sqrt{(A)}+0.28\times\sqrt{(B)}+0.70\times\ln(C)+0.014\times(D)$

<Calculation formula when a CRP value is used>

$DAS28\text{-}4(CRP) = 0.56\times\sqrt{(A)}+0.28\times\sqrt{(B)}+0.36\times\ln((E\times10)+1)+0.014\times(D)+0.96$

9.6. Calculation formula for CDAI

CDAI score = tender joint count (28) + swollen joint count (28) + VAS by patient (cm) + VAS by doctor (cm)

9.7. Calculation formula for SDAI

SDAI score = tender joint count (28) + swollen joint count (28) + VAS by patient (cm) + VAS by doctor (cm) + CRP (mg/dL)

9.8. Handling of patients transferred to another hospital

For patients transferred to another hospital, a person in charge of analysis will link and process CRF data based on information about patients transferred to another hospital received from DM in external file format. Analysis should be conducted with the use of data for which linking process has been completed.

9.9. Descriptive statistics

The followings should be calculated for categorical data and quantitative data.

Type of data	Items to be calculated
Categorical data	Number of patients, percentage, etc.
Quantitative data	Number of patients, mean value, standard deviation, median value, minimum value, maximum value, first quartile, third quartile

9.10. Basic rules for tabulation

Matter	Rule
Tabulation software	Microsoft Excel
Size of printed pages	It should be able to output analysis results onto A4 paper.
Composition	The first sheet should be the cover page. The cover page should include the product name, survey title, type of analysis, and date created. The second sheet should be a list of diagrams. The list of diagrams should include diagram numbers, titles of analysis results, and analysis sets. *Provide link to corresponding figures. On the third and subsequent sheets, diagrams should be created in the order presented in the list of diagrams (Sheet numbers should be diagram numbers).
Matters concerning spaces, punctuations, wording, etc.	Punctuations: Two-byte punctuations should be “, ” and “。”. One-byte punctuations should be “,” and “.”. Katakana: All characters should be two-byte. Alphabet: All characters should be one-byte, and a capital letter should be used at the beginning of a sentence where an alphabet is used. Brackets: All brackets should be two-byte. One-byte spaces Space needed: Between a number and a unit, before and after “/” (other than units and fractions), before and after arithmetic symbols (+ - × ÷ =) Space not needed: Between a number and %, before and after ~, before and after a slash “/” (units and fractions), a hyphen “-”
Diagram numbers and titles	Diagram numbers should be based on “1” in the heading and starts from No. 1 in each figure and table in that heading (e.g. Tables 1.1, 1.2, etc.). For all diagram numbers and titles, the font should be MS Mincho and the

Matter	Rule
	font size should be 10.5 pt. For all table titles in each Appended Form, the font should be MS Mincho and the font size should be 12 pt. In all tables, the font should be MS Mincho and the font size should be 9 to 10.5 pt. In all footnotes, the font should be MS Mincho and the font size should be 9 pt. Ruled lines should be 0.5-pt solid lines (double lines should not be used). In all footnotes to figures, the font should be MS Mincho and the font size should be 9 pt.
Analysis set	The name of the analysis set and the number of patients included should be specified.
Footnotes	Where it is considered necessary to provide an explanation in association with preparation of analysis results, provide the explanation in a footnote. Footnotes should be in the following form: Add a superscript "*sequential number" on the right side of a term, etc. that you want to explain, and provide the "*sequential number" corresponding to the footnote and the explanation under the diagram.
Percentage	When a percentage is calculated, the denominator should be the number of patients in the analysis set. *Specify in a footnote when the denominator used for calculation of a percentage in the same table is different from the number of patients in the analysis set. When percentages for a breakdown of a factor or item are calculated, ensure that the total becomes 100%. Any item redundantly counted should be specified in a footnote.
Context of numbers	When a figure such as a patient composition figure is created, all numbers required to maintain consistency of the context of numbers should be provided.

9.11. Digits of numerical values to be displayed

Digits of numerical values should be as shown below.

Type of numerical value	Digits to be displayed
Mean value, standard deviation, median value, first quartile, third quartile, 95% confidence interval	Figures should be rounded to the significant digits of the data +2 digit and displayed as the significant digit of the data +1 digit
Minimum and maximum values	Figures should be displayed with the same number of digits as the displayed digits of the data

Type of numerical value	Digits to be displayed
Number of patients	Figures should be displayed as integer values
Percentage	Figures should be rounded to the first decimal place and displayed to one place of decimal However, it should be specified in the analysis result output sheet when figures in Appended Form 2 and the incidence rates of adverse events, etc. are rounded to the second decimal place and displayed to two places of decimal.
p value	Figures should be rounded down to the fourth decimal place and displayed to four places of decimal However, figures smaller than 0.0001 should be displayed as <0.0001 without exception

9.12. Rules for displaying numerical values

Case	Display rule
When a figure cannot be calculated	Hyphen "-"
When displaying blank	If any analysis result should be displayed as blank, it should be specified in a footnote what blank indicates

9.13. Test methods

In this analysis plan, a paired t-test should be conducted for the amount of change from before the start of administration. For the incidence rates and remission rates (DAS28) of adverse reactions for each background factor, Fisher's exact test or Mann-Whitney U test should be conducted. Tests should not include an unknown/unspecified category.

9.14. Level of significance

In principle, the significance level of statistical analyses used in this survey is two-sided 5%. $p<0.05$ (<5%) should be considered significant.

9.15. Diagram-specific rules

1) Appended Form 2, Appended Form 10, Appended Form 3
   A) Forms should be created in accordance with the latest version of "Guidance for Application for Reexamination, Japan Pharmaceutical Information Center".
   B) Separation of the reporting period for Appended Form 2 and Appended Form 10 is as follows.
   In principle, this should be the survey unit period defined in the analysis implementation schedule. However, when the size of the printed page does not fit into A4, the period should be determined upon consultation with the entrustor.

10. Data derivation and calculation methods

10.1. General

Name of data	Derivation and calculation methods
Age	Use the age shown in the CRF.
Number of investigating facilities	Aggregate the data for each facility code (DCF code).
Number of patients surveyed	Number of patients included in the safety analysis set.
Start date of Humira treatment	Of the start dates of treatment provided in "2. Status of Humira treatment", the earliest date will be the start date of Humira treatment in each patient. (See "External file for provision of analysis")
End date of Humira treatment	The latest date sorted by the end dates of treatment provided in "2. Status of Humira treatment" will be the end date of Humira treatment in each patient. (See "External file for provision of analysis") In the case of ongoing patients, the date on which the final dosing was completed, which is provided in the CRF, will be the end date of Humira treatment. However, in patients whose end date of Humira treatment is "ongoing" or where the end date of Humira treatment calculated as above exceeds the start date of Humira treatment + 168 days, the end date of Humira treatment should be the start date of Humira treatment + 168 days.
Days to the date on which the last dosing of Humira was completed	End date of Humira treatment - Start date of Humira treatment + 1
Treatment status (total number of doses, total dose)	・ Total number of doses (1) Data on "start date of treatment" and "number of doses" in "2. Status of Humira treatment" should be sorted in the order they are written. (2) Dosing intervals should be calculated for each data on treatment status. The intervals should be 14 days if "biweekly" is checked. If not, the intervals should be obtained from "External file for provision of analysis". (3) The number of doses should be calculated for each data on treatment status. Number of doses = (end date of treatment [after complementation] - start date of treatment [after complementation])/dosing intervals (days) *The end date of treatment in the last record should be the end date of Humira treatment. (4) If the result of (3) is ">0" (greater than 0) and "<1" (smaller than

Name of data	Derivation and calculation methods
	1), it should be 1. If ">=1" (1 or greater), the number should be rounded down to the nearest integer. (5) The total number of doses should be the sum of (4) for each patient. ・ Total dose (1) If the dose of Humira is "other", it should be obtained from "External file for provision of analysis". (2) Doses should be calculated for each data on treatment status. Dose = number of doses x dose (3) The total dose should be the sum of (2) for each patient. ・ Mean dose Mean dose = total dose / total number of doses
Discontinued patients	When the end date of Humira treatment is less than 24 weeks (168 days) after the start date of Humira treatment, the patient should be handled as a discontinued patient.
Reason for discontinuation	In the case of discontinued patients, data should be derived from "Reason for discontinuation" under "3. Discontinuation of treatment" of the CRF or "External file for provision of analysis". If any data have not been provided, it should be handled as "unknown/unspecified". "Onset of an adverse event" should apply only when "Onset of an adverse event" is selected and an adverse event during the safety analysis period has occurred.
Date of discontinuation of treatment	In the case of discontinued patients, the end date of Humira treatment should be the date of discontinuation. Where the start date of Humira treatment + 168 days > the end date of Humira treatment, the end date of Humira treatment should be the date of discontinuation.
Patients switched to other biological products	Patients falling under discontinued patients, for whom "Switching to another drug" is selected for "Treatment status after discontinuation" under "3. Discontinuation of treatment" of the CRF and whose "Drug name" falls under codes of biological products listed in "Drug code list_20171012.xlsx".
Reason for switching	In the case of patients switched to other biological products, data should be derived from "Reason for discontinuation" under "3. Discontinuation of treatment" of the CRF or "External file for provision of analysis". If any data have not been provided, it should be handled as "unknown/unspecified". "Onset of an adverse event" should apply only when "Onset of an adverse event" is selected and an adverse event during the safety analysis period has occurred.

Name of data	Derivation and calculation methods
Status of complications	"With complication" should be selected when the patient has any of the diseases listed under "Complications" in the CRF, "unknown/unspecified" should be selected when "Status of complications" in the CRF is not specified or indeterminable, and "without complication" should be selected otherwise.
Past medical history	"With past medical history" should be selected when the patient has any of the diseases listed under "Past medical history" in the CRF, "unknown" should be selected when "Past medical history" in the CRF is "unknown" or unspecified or indeterminable, and "without past medical history" should be selected otherwise.
Complication: Liver disorder	"With liver disorder" should be selected when the patient has data for "hepatitis", "hepatitis virus carrier", "hepatic cirrhosis", "hepatic steatosis" or "other" in "Complications/Liver disorder" in the CRF, "unknown/unspecified" should be selected when "Status of complications" is not specified or indeterminable, and "without liver disorder" should be selected otherwise.
Complication: Renal disorder	"With renal disorder" should be selected when the patient has data for "nephritis", "renal failure", "nephrotic syndrome" or "other" in "Complications/Renal disorder" in the CRF, "unknown/unspecified" should be selected when "Status of complications" is not specified or indeterminable, and "without renal disorder" should be selected otherwise.
Complication: Cardiovascular disorder	"With cardiovascular disorder" should be selected when the patient has data for "arrhythmia", "Kawasaki's disease", "hypertension" or "other" in "Complications/Cardiovascular disorder" in the CRF, "unknown/unspecified" should be selected when "Status of complications" is not specified or indeterminable, and "without cardiovascular disorder" should be selected otherwise.
Complication: Blood disorder	"With blood disorder" should be selected when the patient has data for "aplastic anaemia", "anaemia", "pancytopenia" or "other" in "Complications/Blood disorder" in the CRF, "unknown/unspecified" should be selected when "Status of complications" is not specified or indeterminable, and "without blood disorder" should be selected otherwise.
Complication: Respiratory disorder	"With respiratory disorder" should be selected when the patient has data for "asthma", "interstitial pneumonia", "obstructive pulmonary disease", "bacterial bronchopneumonia", "non-tuberculous mycobacteriosis (including colonization)" or "other" in "Complications/Respiratory disorder" in the CRF or "External file for provision of analysis", "unknown/unspecified" should be selected when "Status of complications" is not specified or indeterminable, and "without respiratory disorder" should be selected otherwise.

Name of data	Derivation and calculation methods
Complication: Other	"With complication other" should be selected when the patient has data for "iritis", "diabetes mellitus", "gastrointestinal disorder", "osteoporosis", "malignant tumour", "collagen disorder" or "other" in "Complications/Other" in the CRF or "External file for provision of analysis", "unknown/unspecified" should be selected when "Status of complications" is not specified or indeterminable, and "without complication other" should be selected otherwise.
History of allergy	"With a history of allergy" should be selected when any item listed in "History of allergy" in the CRF is checked, "unknown/unspecified" should be selected when "History of allergy" in the CRF is "unknown" or unspecified or indeterminable, and "without a history of allergy" should be selected otherwise.
Patients infected with hepatitis B virus	Patients falling under any of the following are defined as infected with hepatitis B virus. ・A patient has data for "hepatitis" and "viral hepatitis B" in "Complications" in the CRF. ・A patient has data for "hepatitis virus B carrier" in "Complications" in the CRF. ・A patient whose "Complications" in the CRF falls under the MedDRA PT code listed in "Patients infected with hepatitis B virus_for final reporting". ・A patient is negative for "HBs antigen test" or "HBs antibody test" in "Hepatitis B viral test" in the registration form.
Self-administration	In "2. Status of Humira treatment" in the registration form, administration is "self-administration" at all timings.
Self-administration ⇔ administration by a doctor	In "2. Status of Humira treatment" in the registration form, administration is "self-administration" at some timings and "administration by a doctor" at other timings.
Administration by a doctor	In "2. Status of Humira treatment" in the registration form, administration is "administration by a doctor" at all timings.
Dosage and administration category: Dose increase group (20 mg → 40 mg)	In "2. Status of Humira treatment" in the registration form, "dose" was increased from 20 mg to 40 mg.
Dosage and administration category: Maintained dose group	In "2. Status of Humira treatment" in the registration form, "dose" was never increased or reduced.
Dosage and administration category: Other	In "2. Status of Humira treatment" in the registration form, "dose" was reduced to below 20 mg, "dose" was increased from 40 mg to 80 mg, "dose" was increased and then reduced, or "number of doses" is other than biweekly.
Patients deviated from	Patients who received Humira at a dose other than "20 mg/2 weeks"

Name of data	Derivation and calculation methods
recommended dosage and administration of Humira	or "40 mg/2 weeks" are defined as patients deviated from the recommended dosage and administration.
Previous medications	Of the drugs listed under "Status of administration of concomitant drugs" in "5. Previous medications for juvenile idiopathic arthritis" in the CRF and confirmed to have been administered between the start date of Humira treatment - 90 days and the start date of Humira treatment - 1 day, drugs falling under "MTX", "DMARDs", "steroid (oral + injection)" or "NSAIDs (oral + injection)" in "Drug code list_20171012.xlsx" are defined as previous medications.
Status of previous medications	"With previous medications" should be selected when the patient was previously treated with medications, "unknown/unspecified" should be selected when "Status of previous medications for juvenile idiopathic arthritis" is not specified or indeterminable, and "without previous medications" should be selected otherwise.
Previous medication: Methotrexate	"With previous medication: methotrexate" should be selected when the conditions for "previous medications" are met and the previous medication falls under "MTX" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of previous medications is "unknown/unspecified", and "without previous medication: methotrexate" should be selected otherwise.
Previous medication: Corticosteroid	"With previous medication: corticosteroid" should be selected when the conditions for "previous medications" are met and the previous medication falls under "steroid (oral + injection)" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of previous medications is "unknown/unspecified", and "without previous medication: corticosteroid" should be selected otherwise.
Previous medication: NSAIDs	Drugs that meet the conditions for "previous medications" and fall under "NSAIDs (oral + injection)" in "Drug code list_20171012.xlsx".
Previous medication: Other DMARDs	"With previous medication: other DMARDs" should be selected when the drug meets the conditions for "previous medications" and does not fall under "MTX" and falls under "DMARDs" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of previous medications is "unknown/unspecified", and "without previous medication: other DMARDs" should be selected otherwise.
Previous medication (biological products)	Drugs listed in "4. History of treatment with biological products for juvenile idiopathic arthritis" (which applies to all biological products previously used) in the CRF should be all previous medications (biological products) confirmed to have been administered between the start date of a biological product and the start date of Humira

Name of data	Derivation and calculation methods
	treatment - 1 day. Alternatively, of the drugs listed under "Status of administration of concomitant drugs" in "5. Previous medications for juvenile idiopathic arthritis" in the CRF and confirmed to have been administered between the start date of Humira treatment - 90 days and the start date of Humira treatment - 1 day, drugs falling under "biological products" in "Drug code list_20171012.xlsx" are defined as previous medications (biological products).
History of treatment with previous medications (biological products)	"With a history of treatment with previous medications (biological products)" should be selected when the patient was previously treated with medications (biological products), "unknown/unspecified" should be selected when "History of treatment with biological products" is not specified or indeterminable, and "without a history of treatment with previous medications (biological products)" should be selected otherwise.
Previous medication (biological product): tocilizumab	"With previous medication (biological product): tocilizumab" should be selected when the drug meets the conditions of "previous medications (biological products)" and the higher order 7 digits of the drug code of the previous medication (biological product) are "6399421", "unknown/unspecified" should be selected when the history of treatment with previous medications (biological products) is "unknown/unspecified", and "without previous medication (biological product): tocilizumab" should be selected otherwise.
Previous medication (biological product): etanercept	"With previous medication (biological product): etanercept" should be selected when the drug meets the conditions of "previous medications (biological products)" and the higher order 7 digits of the drug code of the previous medication (biological product) are "3999424", "unknown/unspecified" should be selected when the history of treatment with previous medications (biological products) is "unknown/unspecified", and "without previous medication (biological product): etanercept" should be selected otherwise.
Previous medication (biological product): other	"With previous medication (biological product): other" should be selected when the drug meets the conditions of "previous medications (biological products)" and the higher order 7 digits of the drug code of the previous medication (biological product) are other than "6399421" and "3999424" and the drug falls under "Biological products" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the history of treatment with previous medications (biological products) is "unknown/unspecified", and "without previous medication (biological product): other" should be selected otherwise.
Concomitant drugs	Concomitant drugs are defined as drugs listed in "5. Previous medications for juvenile idiopathic arthritis", "6. Status of

Name of data	Derivation and calculation methods
	administration of concomitant drugs (1) [Concomitant drugs for juvenile idiopathic arthritis]", "6. Status of administration of concomitant drugs (2) [Other concomitant drugs]" in the CRF and confirmed to have been administered between the start date of Humira treatment and the end date of Humira treatment.
Status of concomitant drugs	"With concomitant drugs" should be selected when the patient is treated with concomitant drugs, "unknown/unspecified" should be selected when "Status of previous medications for juvenile idiopathic arthritis/concomitant drugs for juvenile idiopathic arthritis/other concomitant drugs" is not specified or indeterminable, and "without concomitant drugs" should be selected otherwise.
Concomitant drug: methotrexate	"With concomitant drug: methotrexate" should be selected when the conditions for "concomitant drugs" are met and the concomitant drug falls under "MTX" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of concomitant drugs is "unknown/unspecified", and "without concomitant drug: methotrexate" should be selected otherwise.
Concomitant drug: corticosteroid	"With concomitant drug: corticosteroid" should be selected when the conditions for "concomitant drugs" are met and the concomitant drug falls under "steroid (oral + injection)" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of concomitant drugs is "unknown/unspecified", and "without concomitant drug: corticosteroid" should be selected otherwise.
Concomitant drug: NSAIDs	"With concomitant drug: NSAIDs" should be selected when the conditions for "concomitant drugs" are met and the concomitant drug falls under "NSAIDs (oral + injection)" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of concomitant drugs is "unknown/unspecified", and "without concomitant drug: NSAIDs" should be selected otherwise.
Concomitant drug: other DMARDs	"With concomitant drug: other DMARDs" should be selected when the drug meets the conditions for "concomitant drugs" and does not fall under "MTX" and falls under "DMARDs" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of concomitant drugs is "unknown/unspecified", and "without concomitant drug: other DMARDs" should be selected otherwise.
Concomitant drug: Other drugs	"With concomitant drug: other drugs" should be selected when the drug meets the conditions for "concomitant drugs" and does not fall under "MTX", "steroid (oral + injection)" or "DMARDs" in "Drug code list_20171012.xlsx", "unknown/unspecified" should be selected when the status of concomitant drugs is "unknown/unspecified", and

Name of data	Derivation and calculation methods
	"without concomitant drug: other drugs" should be selected otherwise.
Tuberculin reaction	Related data should be derived from "Tuberculin skin test" in the registration form.
Quantiferon test (including T-SPOT)	Related data should be derived from "Quantiferon test", "External file for provision of analysis (a list of T-SPOT)" in the registration form.
Chest x-ray	When the date of chest x-ray between the start date of Humira treatment - 90 days and the start date of Humira treatment is provided in "8. Occurrence of tuberculosis and serious respiratory disorder" in the registration form, the patient is defined as those who underwent chest x-ray.
Chest CT	When the date of chest CT between the start date of Humira treatment - 90 days and the start date of Humira treatment is provided in "8. Occurrence of tuberculosis and serious respiratory disorder" in the registration form, the patient is defined as those who underwent chest CT.
Prophylactic administration (status of prophylactic administration by implementation status of tuberculosis tests)	Related data should be derived from "prophylactic administration or antituberculosis drugs" in the registration form.
Status of combination therapy for juvenile idiopathic arthritis	"With combination therapy for juvenile idiopathic arthritis" should be selected when data is provided for "7. Non-drug combination therapy for juvenile idiopathic arthritis" in the CRF, "unknown/unspecified" should be selected when "Status of combination therapy" is not specified or indeterminable, and "without combination therapy" should be selected otherwise.
Combination therapy for juvenile idiopathic arthritis: rehabilitation	The detail of combination therapy falls under "Contents of implementation/rehabilitation" in the "External file for provision of analysis".
Combination therapy for juvenile idiopathic arthritis: other	The detail of combination therapy falls under "Contents of implementation/other" in the "External file for provision of analysis".
Combination therapy for juvenile idiopathic arthritis: unknown/unspecified	The detail of combination therapy falls under "Contents of implementation/unknown, unspecified" in the "External file for provision of analysis".
Dose of concomitant drug methotrexate per body surface area	In the case of concomitant drug methotrexate, body surface area should be calculated with the use of data before the start of treatment in "9. Clinical course" in the CRF and the dose of methotrexate per

Name of data	Derivation and calculation methods
	body surface area should be calculated. $S=W^{0.425}\times H^{0.725}\times 71.84$ S = body surface area (cm2); W = body weight from the start date of Humira treatment - 28 days to the start date of Humira treatment (kg); H = height from the start date of Humira treatment - 28 days to the start date of Humira treatment (cm) If the dose of methotrexate was changed during the survey period, calculate doses per body surface area for each record and calculate the mean value.

10.2. Safety analysis

Name of data	Derivation and calculation methods
Adverse events	For adverse event-related data, "an AE matching list", the data set through the AE matching activities (matching of CRF data and safety information data), should be used. Adverse events with the same case number should be counted as one event when the PT is the same. See the definition document for analytical dataset as aggregation of adverse events is conducted at the time of the creation of analytical dataset. Name of analytical dataset: A_AE Name of variable: AETERM
Seriousness of adverse events	For seriousness of adverse events aggravated from a single patient as the same PT, seriousness of the company-determined CRF data set though the AE matching activities should be set in the following order of priority: (1) Serious (2) Non-serious See the definition document for analytical dataset as setting of seriousness of adverse events is conducted at the time of the creation of analytical dataset. Name of analytical dataset: A_AE_AL Name of variable: AESERS
Causal relationship of adverse events	Where the causal relationship set through AE matching is other than "not related", the causal relationship is defined as related. For causal relationship of an adverse event aggravated from a single patient as the same PT, causal relationship set through AE matching activities should be set in the following order of priority: (2) Related (2) Not related See the definition document for analytical dataset as setting of causal relationship of adverse events is conducted at the time of the creation of analytical dataset. Name of analytical dataset: A_AE_AL

Name of data	Derivation and calculation methods
	Name of variable: AERELS
Outcomes of adverse events	Outcomes of adverse events aggravated from a single patient as the same PT should be set in the following order of priority: (1) Fatal (2) Unknown (3) Not recovered/not resolved (4) Recovered/resolved with sequelae (5) Recovering/resolving (6) Recovered/resolved (7) Unspecified See the definition document for analytical dataset as setting of outcomes of adverse events is conducted at the time of the creation of analytical dataset. Name of analytical dataset: A_AE_AL Name of variable: AEOUTS
Timing of onset of adverse events	With the start date of treatment as Day 1 Adverse events that occurred after the start of treatment and within 4 weeks of treatment (Days 1 to 28) Adverse events that occurred after Week 4 of treatment and within 8 weeks of treatment (Days 29 to 56) Adverse events that occurred after Week 8 of treatment and within 12 weeks of treatment (Days 57 to 84) Adverse events that occurred after Week 12 of treatment and within 16 weeks of treatment (Days 85 to 112) Adverse events that occurred after Week 16 of treatment and within 20 weeks of treatment (Days 113 to 140) Adverse events that occurred after Week 20 of treatment and within 24 weeks of treatment (Days 141 to 168) Occurrence of adverse events after the end of treatment: Adverse events that occurred at and after Week 24 of treatment (on and after Day 169)
Adverse events occurred during treatment	Adverse events that occurred after the start date of Humira treatment by the end date or the date of discontinuation of Humira treatment
Adverse events occurred after treatment	Adverse events that occurred after the end date or the date of discontinuation of Humira treatment by the start date of Humira treatment + 196 days
Serious adverse events	Adverse events whose seriousness set through the AE matching activities is “serious” are defined as serious adverse events.
Adverse reactions	Adverse events whose causal relationship is other than “not related” based on company-determined data set through the AE matching activities are defined as adverse reactions. Adverse reactions with the same case number should be counted as one event when the PT is the same. Name of analytical dataset: A_AE_AL Names of variables: AERELS, AESOCCD, AEPTCD

10.3. Efficacy analysis

<table>
<tr><th>Name of data</th><th>Derivation and calculation methods</th></tr>
<tr><td>Improvement in DAS28-4/ESR by EULAR Response Criteria</td><td>
Improvement in DAS28-4/ESR should be calculated in accordance with EULAR Response Criteria.

EULAR Judgment criteria for improvement in DAS28 (4/ESR)
<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="3">Improvement in DAS28[#1]</th></tr>
<tr><th>>1.2</th><th>>0.6 and ≤1.2</th><th>≤0.6</th></tr>
<tr><td rowspan="3">DAS28 at the time of assessment</td><td>≤3.2</td><td>Good response</td><td>Moderate response</td><td>No response</td></tr>
<tr><td>>3.2 and ≤5.1</td><td>Moderate response</td><td>Moderate response</td><td>No response</td></tr>
<tr><td>>5.1</td><td>Moderate response</td><td>No response</td><td>No response</td></tr>
</table>
[#1]Improvement in DAS28: (DAS28 at the start of Humira treatment) - (DAS28 at the time of assessment)
Good Response and Moderate Response should be considered effective, and No Response as ineffective.
</td></tr>
<tr><td>Remission</td><td>
For DAS28-4/ESR, CDAI and SDAI, cases meeting the following conditions should be handled as remission.
・ Where DAS28-4/ESR is <2.6, remission is “Yes”.
・ Where CDAI is ≤2.8, remission is “Yes”.
・ Where SDAI is ≤3.3, remission is “Yes”.
See the definition document for analytical dataset as setting of the presence or absence of efficacy is conducted at the time of the creation of analytical dataset.
Name of analytical dataset: A_EFF2
Names of variables: AVAL_ESR_1, AVAL_CDAI, AVAL_SDAI
</td></tr>
<tr><td>DAS28 disease activity</td><td>
For DAS28-4/ESR, categories of disease activity are shown as follows:
・ Remission DAS28-4/ESR <2.6
・ Low disease activity: 2.6 <=DAS28-4/ESR <3.2
・ Moderate disease activity: 3.2 <=DAS28-4/ESR <5.1
・ High disease activity: 5.1 <=DAS28-4/ESR
Name of analytical dataset: A_EFF2
Name of variable: AVAL_ESR_1
</td></tr>
</table>

11. Data-layer separation

Data	Layer separation
Reason for discontinuation	Remission, subtherapeutic response, onset of adverse events, patient's request, no hospital visit (including hospital transfer), other
Reason for switching	Remission, subtherapeutic response, onset of adverse events, patient's request, no hospital visit (including hospital transfer), other
Sex	Male, female, unknown/unspecified
Pregnancy/breastfeeding	Not pregnant/breastfeeding, pregnant, breastfeeding, unknown/unspecified
Age 1	≤6 years, >6 years
Age 2	<15 years, ≥15 years and <65 years, ≥65 years
Age 3	<6 years, ≥6 years and <11, ≥11 years and <16 years, ≥16 years and <21 years, ≥21 years
Body weight	<15 kg, ≥15 kg and <30 kg, ≥30 kg, unknown/unspecified
BMI(kg/m^2)	<18.5 kg/m^2, ≥18.5 kg/m^2 and <25.0 kg/m^2, ≥25.0 kg/m^2 and <30.0 kg/m^2, ≥30.0 kg/m^2 and <35.0 kg/m^2, ≥35.0 kg/m^2, unknown
Inpatient/outpatient status at the start of Humira treatment	Inpatient, outpatient, unknown/unspecified
Reason for use and type of disease	Generalised arthritis, oligoarthritis (persistent), oligoarthritis (extended), polyarthritis (RF negative), polyarthritis (RF positive), other, unknown/unspecified
Disease duration 1	<6 months, ≥6 months and <1 year, ≥1 year and <2 years, ≥2 years and <3 years, ≥3 years and <5 years, ≥5 years and <10 years, ≥10 years and <20 years, ≥20 years, unknown/unspecified
Disease duration 2	<5 years, ≥5 years, unknown/unspecified
Race	Japanese, other, unknown/unspecified
Steinbrocker Staging System	Stage I, Stage II, Stage III, Stage IV, unknown/unspecified
Steinbrocker Functional Classification	Class I, Class II, Class III, Class IV, unknown/unspecified
Administration method category	Self-administration, self-administration ⇔ administration by a doctor, administration by a doctor, unknown/unspecified
Past medical history	No, yes, unknown/unspecified
Complications	No, yes, unknown/unspecified
Breakdown of complications	Liver disorder, renal disorder, cardiovascular disorder, blood disorder, respiratory disorder, other
Complication: Liver disorder	No, yes, unknown/unspecified
Complication: Renal	No, yes, unknown/unspecified

Data	Layer separation
disorder	
Complication: Cardiovascular disorder	No, yes, unknown/unspecified
Complication: Blood disorder	No, yes, unknown/unspecified
Complication: Respiratory disorder	No, yes, unknown/unspecified
Complication: Other	No, yes, unknown/unspecified
History of allergy	No, yes, unknown/unspecified
Breakdown of history of allergy	Drug, food, other
Previous medications	No, yes, unknown/unspecified
Breakdown of previous medications	Methotrexate, corticosteroid, NSAIDs, other DMARDs
History of treatment with previous medications (biological products)	No, yes, unknown/unspecified
Breakdown of history of treatment with previous medications (biological products)	Tocilizumab, etanercept, other
Concomitant drugs	No, yes, unknown/unspecified
Breakdown of combination drugs	Methotrexate, corticosteroid, NSAIDs, other DMARDs, other drugs
Tuberculin skin test	Tested, not tested, unknown/unspecified
Quantiferon test (including T-SPOT)	Tested, not tested, unknown/unspecified
Chest x-ray	Tested, not tested, unknown/unspecified
Chest CT	Tested, not tested, unknown/unspecified
Immunology test (tuberculin skin test or Quantiferon test or T-SPOT)	No, yes, unknown/unspecified
Image testing (chest x-ray or chest CT)	No, yes, unknown/unspecified
Prophylactic administration (status of prophylactic administration by	No, yes, unknown/unspecified

Data	Layer separation
implementation status of tuberculosis tests)	
HBs antigen test	Implemented (negative, positive, unknown/unspecified, subtotal), not implemented, unknown/unspecified
HBs antibody test	Implemented (negative, positive, unknown/unspecified, subtotal), not implemented, unknown/unspecified
HBc antibody test	Implemented (negative, positive, unknown/unspecified, subtotal), not implemented, unknown/unspecified
Status of Humira treatment (dosage and administration)	20 mg/2 weeks, 40 mg/2 weeks, 20 mg/2 weeks → 40 mg/2 weeks, other
Number of doses	≥1 to <2 doses, ≥2 to <6 doses, ≥6 to <12 doses, ≥12 doses
Days to the date of the last dosing	1 to 28 days, 29 to 84 days, 85 to 168 days, ongoing at day 169
Dose at the start of Humira treatment	20 mg, 40 mg, 80 mg, other, unknown/undescribed
Dosage and administration category	Dose increase group (20 mg → 40 mg), maintained dose group, other, unknown/unspecified
Self-administration	No, yes, unknown/unspecified
Error caused by self-administration	No, yes, unknown/unspecified
Priority survey item	Infection, tuberculosis, interstitial pneumonia, malignant tumour, congestive cardiac failure, autoimmune disease, pancytopenia, demyelinating disease, administration site reaction
Status of previous medication: biological products	No, yes, unknown/unspecified
Status of previous medication: MTX	No, yes, unknown/unspecified
Status of previous medication: corticosteroid	No, yes, unknown/unspecified
Status of previous medication: NSAIDs	No, yes, unknown/unspecified
Status of previous medication: Other DMARDs	No, yes, unknown/unspecified
Status of concomitant drug: MTX	No, yes, unknown/unspecified
Status of MTX: details	<4 mg/m^2/week, ≥4 mg/m^2/week and <7 mg/m^2/week, ≥7 mg/m^2/week

Data	Layer separation
	and <10 mg/m^2/week, ≥10 mg/m^2/week, dose per body surface area unknown
Status of concomitant drug: corticosteroid	No, yes, unknown/unspecified
Status of concomitant drug: NSAIDs	No, yes, unknown/unspecified
Status of concomitant drug: Other DMARDs	No, yes, unknown/unspecified
Combination therapy for juvenile idiopathic arthritis	No, yes, unknown/unspecified
Combination therapy for juvenile idiopathic arthritis: details	Rehabilitation, other, unknown/undescribed
Duration of combination use of MTX for juvenile idiopathic arthritis	No, yes, unknown/unspecified
Duration of combination use of MTX for juvenile idiopathic arthritis: details	After the start of Humira treatment up to the end date of Humira treatment, at least a dose used during Humira treatment, unknown/unspecified
Timing of onset of adverse events	From the start of treatment and within 4 weeks of treatment, after Week 4 of treatment and within 8 weeks of treatment, after Week 8 of treatment and within 12 weeks of treatment, after Week 12 of treatment and within 16 weeks of treatment, after Week 16 of treatment and within 20 weeks of treatment, after Week 20 of treatment and within 24 weeks of treatment, after Week 24 of treatment

12. Handling of data on tests/timing of assessment

Timing and period category	Handling of data
Time window for efficacy assessment	Before the start of treatment: from the start date of Humira treatment - 30 days to the start date of Humira treatment At Week 4 of treatment: from the start date of Humira treatment + 1 day to the start date of Humira treatment + 42 days At Week 8 of treatment: from the start date of Humira treatment + 43

Timing and period category	Handling of data
	days to the start date of Humira treatment + 70 days At Week 12 of treatment: from the start date of Humira treatment + 71 days to the start date of Humira treatment + 98 days At Week 16 of treatment: from the start date of Humira treatment + 99 days to the start date of Humira treatment + 140 days At Week 24 of treatment: from the start date of Humira treatment + 141 days to the start date of Humira treatment + 196 days At the final assessment: the data measured at the end during the period from the start date of Humira treatment + 1 day to the start date of Humira treatment + 196 days.

13. Diagrams to be created (numbers and names of diagrams)

13.1. General

"Figure 1.1 Patient disposition diagram"

Analysis object: Enrolled patients

Purpose of analysis: The number of patients enrolled, number of facilities contracted, number of clinical departments contracted, number of patients with fixed CRFs, number of patients with uncollectible CRFs, number of patients included in the safety analysis set, number of patients excluded from the safety analysis set, number of patients included in the efficacy analysis set, and number of patients excluded from the efficacy analysis set will be calculated. Furthermore, breakdowns of reasons for patients excluded from the safety analysis set and patients excluded from the efficacy analysis set will be calculated.

Note: For a reason for exclusion to which no patient falls under, the entire item should not be output.

"Figure 1.2 Breakdown of patients included in the safety analysis set"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For patients included in the safety analysis set, number of patients included in the efficacy analysis set (DAS28-4CRP), number of patients who cannot be assessed with DAS28-4CRP, number of patients included in the efficacy analysis set (CDAI), number of patients who cannot be assessed with CDAI, number of patients included in the efficacy analysis set (SDAI), number of patients who cannot be assessed with SDAI, number of patients included in the efficacy analysis set (DAS28-4/ESR), and number of patients who cannot be assessed with DAS28-4/ESR will be calculated for each efficacy endpoint.

Note: This table will be output on a separate sheet as an appendix to Figure 1.1 Patient composition diagram when the aggregate results in Figure 1.1 is output.

"Table 1.1 Aggregate results of discontinuation of treatment"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: For patients who discontinued treatment and the breakdown of the reasons for discontinuation (remission, subtherapeutic response, onset of adverse events, patient's request, no hospital visit [including hospital transfer], other), the number and percentage of patients will be calculated.

Notes:
- The breakdown of the reasons for discontinuation may be redundantly aggregated.
- The denominator of the percentage of patients who discontinued treatment should be patients included in the safety analysis set, and the denominator of the percentage in the breakdown of the reasons for discontinuation should be patients who discontinued treatment as defined in "10.1 General".
- "Onset of an adverse event" should apply only when "Onset of an adverse event" is selected and an adverse event during safety analysis period has occurred.

"Table 1.2 Aggregate results of switching to other biological products"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: For the number of patients switched to other biological products and the breakdown of the reasons for switching (remission, subtherapeutic response, onset of adverse events, patient's request, no hospital visit [including hospital transfer], other), the number and percentage of patients will be calculated.

Notes:
- The breakdown of the reasons for switching may be redundantly aggregated.
- The denominator of the percentage of switched patients should be patients included in the safety analysis set, and the denominator of the percentage in the breakdown of the reasons for switching should be patients switched to other biological products as defined in "10.1 General".
- "Onset of an adverse event" should apply only when "Onset of an adverse event" is selected and an adverse event during safety analysis period has occurred.

"Table 1.3 Aggregate results of patient background"

Analysis object: Patients included in the safety analysis set, patients included in the efficacy analysis set

Purpose of analysis: The number and percentage of patients by patient background will be calculated. For quantitative data, basic statistics will also be calculated.

Patient background should follow "11. Data-layer separation" (sex, pregnancy/breastfeeding, age 1, age 2, age 3, body weight, BMI, inpatient/outpatient status at the start of Humira treatment, reason for use and type of disease, disease duration 1, disease duration 2, race, Steinbrocker Staging System, Steinbrocker Functional Classification, administration method category, past medical history, complications, breakdown of complications, history of allergy, breakdown of history of allergy, previous medications, breakdown of previous medications, history of treatment with previous

medications [biological products], breakdown of history of treatment with previous medications [biological products], concomitant drugs, breakdown of concomitant drugs, of the breakdown of concomitant drugs, dose of methotrexate per body surface area, concomitant drug [methotrexate], breakdown of concomitant drug [methotrexate]).

Notes:
- The denominator of the percentage of patients falling under pregnancy/breastfeeding should be "female" (sex) patients.
- The denominators of percentages in items other than the above should be the upper-rank analysis set.
- The reason for use and type of disease, breakdown of complications, breakdown of history of allergy, breakdown of previous medications, breakdown of history of treatment with of previous medications (biological products), breakdown of concomitant drugs, and breakdown of concomitant drug (methotrexate) may be redundantly aggregated.

"Table 1.4 Implementation status of tuberculosis tests (1) (implementation rate of each test)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be calculated for each implementation status (tested, not tested, unknown/unspecified) of tuberculin skin test, Quantiferon test (including T-SPOT), chest x-ray and chest CT before the start of treatment.

Note: None in particular.

"Table 1.5 Implementation status of tuberculosis tests (2) (cross tabulation showing implementation status of tests)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be calculated for each implementation status (no, yes, unknown/unspecified) of immunology test (tuberculin skin test or Quantiferon test or T-SPOT) and imaging procedure (chest x-ray or chest CT) before the start of treatment.

Note: None in particular.

"Table 1.6 Implementation status of prophylactic administration"

Analysis object: Of patients included in the safety analysis set, those who underwent tuberculosis tests.

Purpose of analysis: The number and percentage of patients will be calculated for each result of tuberculosis tests (tuberculin test, tuberculin skin test, Quantiferon test [including T-SPOT]) before the start of treatment by implementation status of prophylactic administration of antituberculosis drugs (no, yes, unknown/unspecified).

Notes:
- Involving patients undergoing tuberculosis tests, cross tabulation should be conducted regarding the tuberculosis test results and prophylactic administration of antituberculous drugs.

- For the status of prophylactic administration of antituberculosis drugs, data from the registration forms should be used.
- The result categories of each tuberculosis test are shown below.

Tuberculosis test	Tuberculin skin test	Quantiferon test (including T-SPOT)
Positive	Positive	Positive
		Negative
		Not tested
		Indeterminable
		Unknown/unspecified
	Negative	Positive
	Not tested	Positive
	Unknown/unspecified	Positive
Negative	Negative	Negative
	Negative	Unknown/unspecified
	Negative	Not tested
	Not tested	Negative
	Unknown/unspecified	Negative
Indeterminable	Negative	Indeterminable
	Not tested	Indeterminable
	Unknown/unspecified	Indeterminable
Unknown	Unknown/unspecified	Negative
	Negative	Unknown/unspecified
	Not tested	Unknown/unspecified
	Unknown/unspecified	Not tested

"Table 1.7 Implementation status of hepatitis B tests"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be calculated for each implementation status (tested, not tested, unknown/unspecified) of hepatitis B test (HBs antigen test, HBs antibody test, HBc antibody test). Where tests were performed, the number and percentage of patients will also be calculated for breakdown of their results (negative, positive, unknown/unspecified).

Note: None in particular.

"Table 1.8 Status of Humira treatment (dosage and administration)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: For the status of Humira treatment (dosage and administration) (20 mg/2 weeks, 40 mg/2 weeks, 20 mg/2 weeks → 40 mg/2 weeks, other), the number and percentage of patients will be calculated.

Note: Patients who received doses other than "20 mg/2 weeks", "40 mg/2 weeks", "20 mg/2 weeks

→ 40 mg/2 weeks" should be categorized into "other".

"Table 1.9 Status of Humira treatment (number of doses, days to the date of the last dosing)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: For the status of Humira treatment (number of doses, days to the date of the last dosing), the number and percentage of patients will be calculated by category defined in "11. Data-layer separation".

Note: Where the last record of the treatment status is checked for "ongoing" or where the end date of treatment exceeds the start date of treatment + 168 days, the end date of treatment should be handled as the start date of treatment + 168 days.

"Table 1.10 Dose by body weight at the start of treatment"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be calculated for each category of dose at the start of Humira treatment as defined in "11. Data-layer separation" (number of doses, days to the date of the last dosing) by body weight at the start of Humira treatment (<15 kg, ≥15 kg and <30 kg, ≥30 kg, unknown/unspecified).

Note: The denominator of the percentage of the number of patients should be patients included in the safety analysis set.

"Table 1.11 Incidence rate of administration errors caused by self-injection"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be aggregated by the status of self-administration (no, yes, unknown/undescribed). Where self-administration was conducted, the number and percentage of patients will be calculated for each category of errors caused by self-administration defined in "11. Data-layer separation" (self-administration, errors caused by self-administration).

Notes: The denominator of the percentage of errors caused by self-administration should be patients who conducted self-administration ("yes").

"Table 1.11.1 Incidence rate of administration errors caused by self-injection (by age)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be calculated for "11. Data-layer separation" (age category 3) by the status of self-administration (no, yes, unknown/undescribed).

Where self-administration was conducted, the number and percentage of patients will be calculated for each age category (age category 3) by category of errors caused by self-administration defined in "11. Data-layer separation" (self-administration, errors caused by self-administration).

Notes: The denominator of the percentage of errors caused by self-administration should be patients

who conducted self-administration (“yes”).

13.2. Safety

“Table 2.1 Appended Form 2”

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Involving adverse events during the safety analysis period, the following items will be aggregated by period.

Number of investigating facilities: Number of facilities included in the survey. When multiple clinical departments in a single facility have been contracted, they should be counted as one facility.

Number of patients surveyed: Number of patients included in the safety analysis set.

Number of patients who experienced adverse reactions, etc.: Number of patients who experienced adverse reactions.

Number of adverse reactions, etc.: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Percentage of patients who experienced adverse reactions, etc. (%): Number of patients who experienced adverse reactions, etc. ÷ number of patients included in the safety analysis set x 100.

Types of adverse reactions, etc.: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Notes:
- The categories of period should be status up to approval, special drug use-results survey, and total.
- The version of MedDRA/J used should be provided.
- Adverse reactions and infections that cannot be expected from “Precautions” in the package insert should be indicated with *.

“Table 2.2 Appended Form 10”

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Involving adverse events during the safety analysis period, the following items will be aggregated by period.

Number of investigating facilities: Number of facilities included in the survey. When multiple clinical departments in a single facility have been contracted, they should be counted as one facility.

Number of patients surveyed: Number of patients included in the safety analysis set.

Number of patients who experienced events: Number of patients who

experienced serious adverse events.

Number of cases: Number of serious adverse events that occurred. When a single patient experienced multiple episodes of the same serious adverse event (PT), they should be counted as one event.

Percentage of patients who experienced events: Number of patients who experienced serious adverse events ÷ number of patients included in the safety analysis set x 100.

Types of serious adverse events: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same serious adverse event (PT), they should be counted as one event.

Notes:
- The categories of period should be status up to approval, drug use-results survey, special drug use-results survey, post-marketing clinical study, and total.
- The version of MedDRA/J used should be provided.
- Adverse events that cannot be expected from "Precautions" in the package insert should be indicated with *.
- The number of events for which the causal relationship was ruled out should be shown in [ ].

"Table 2.3 List of incidence of adverse reactions in this survey"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions or serious adverse reactions during the safety analysis period will be aggregated as follows.

Number of patients surveyed: Number of patients included in the safety analysis set.

Number of patients who experienced adverse reactions (or serious adverse reactions): Number of patients who experienced adverse reactions (or serious adverse reactions).

Number of adverse reactions (or serious adverse reactions): Number of adverse reactions (or serious adverse reactions) that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Percentage of patients who experienced adverse reactions (or serious adverse reactions): Number of patients who experienced adverse reactions (or serious adverse reactions) ÷ number of patients included in the safety analysis set x 100.

Types of adverse reactions (serious adverse reactions): Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should

be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.4 List of incidence of adverse events and adverse reactions by priority survey item"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: For adverse events during the safety analysis period or adverse reactions during the safety analysis period, the number and percentage of patients will be calculated for each priority survey item (infection, tuberculosis, interstitial pneumonia, malignant tumour, congestive cardiac failure, autoimmune disease, pancytopenia, demyelinating disease, administration site reaction) by seriousness (non-serious, serious, overall).

Note: None in particular.

"Table 2.5.1 Incidence of adverse reactions by patient background factor"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Involving adverse reactions during the safety analysis period, the number of patients and the number and percentage of patients who experienced adverse reactions will be calculated in accordance with "11. Data-layer separation" (age 1, age 2, age 3, sex, body weight, BMI, reason for use and type of disease, disease duration 2, complications, complication: liver disorder, complication: renal disorder, complication: cardiovascular disorder, complication: blood disorder, complication: respiratory disorder, complication: other, past medical history, history of allergy, Steinbrocker Staging System, Steinbrocker Functional Classification, administration method category, previous medications, status of previous medication: biological product, status of previous medication: MTX, status of previous medication: corticosteroid, status of previous medication: NSAIDs, status of previous medication: Other DMARDs, concomitant drugs, status of concomitant drug: MTX, status of MTX: details, status of concomitant drug: corticosteroid, status of concomitant drug: NSAIDs, status of concomitant drug: Other DMARDs).

For the incidence rates of adverse reactions, Fisher's exact test should be conducted when the background factor is a nominal scale and Mann-Whitney U test should be conducted when the background factor is an ordinal scale.

Notes: • Reason for use and type of disease may be redundantly aggregated. No test will be conducted for this item.

"Table 2.5.2 Incidence of adverse events in patients switched to other biological products"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Involving adverse events during the safety analysis period, the number of patients, the number and percentage of patients who experienced adverse events will be calculated on the basis of the number of patients switched to

other biological products and the breakdown of the reasons for switching (remission, subtherapeutic response, onset of adverse events, patient's request, no hospital visit [including hospital transfer], other).

Notes: • The breakdown of the reasons for switching may be redundantly aggregated.
• "Onset of an adverse event" should apply only when "Onset of an adverse event" is selected and an adverse event during safety analysis period has occurred.

"Table 2.5.3 Incidence of adverse reactions to combination therapy for juvenile idiopathic arthritis"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Involving adverse reactions during the safety analysis period, the number of patients, the number and the percentage of patients who experienced adverse reactions will be calculated on the basis of combination therapy for juvenile idiopathic arthritis (no, yes, unknown/unspecified). For patients receiving combination therapy, the number of patients, the number and percentage of patients who experienced adverse reactions by breakdown of combination therapy (rehabilitation, other, unknown/unspecified) will be calculated.

Notes: The breakdown of combination therapy may be redundantly aggregated.

"Table 2.5.4 Incidence of adverse reactions by duration of combination use of MTX for juvenile idiopathic arthritis"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Involving adverse reactions during the safety analysis period, the number of patients, the number and the percentage of patients who experienced adverse reactions will be calculated on the basis of duration of combination use of MTX for juvenile idiopathic arthritis (no, yes, unknown/unspecified). Where there is a duration of combination use of MTX, the number of patients, the number and percentage of patients who experienced adverse reactions by breakdown of duration of combination use (after the start of Humira treatment up to the end date of Humira treatment, at least a dose used during Humira treatment, unknown/unspecified) will be calculated.

Notes: The breakdown of duration of combination use may be redundantly aggregated.

"Table 2.5.5.X Examination of factors affecting the occurrence of adverse reactions"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: For factors with a significant difference ($p<0.05$) in "Table 2.5.1", adverse reactions during the safety analysis period will be aggregated by stratification factor as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions (or serious adverse

reactions): Number of patients who experienced adverse reactions (or serious adverse reactions).

Number of adverse reactions (or serious adverse reactions): Number of adverse reactions (or serious adverse reactions) that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions (serious adverse reactions): Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: ・ A form should be created for each factor.
・ The version of MedDRA/J used should be provided.

"Table 2.6 Incidence of adverse reactions by disease type category"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (reason for use and type of disease) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions (or serious adverse reactions): Number of patients who experienced adverse reactions (or serious adverse reactions).

Number of adverse reactions (or serious adverse reactions): Number of adverse reactions (or serious adverse reactions) that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions (serious adverse reactions): Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.7 Incidence of adverse reactions by body weight"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (body weight) as shown below. The number of patients analyzed, the number and percentage of patients who

experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.8 Incidence of adverse reactions by age"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (age 1) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.9 Incidence of adverse reactions in patients who received an increased dose"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (dosage and administration category) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions

by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.10 Incidence of adverse reactions in patients who self-administered Humira"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (self-administration) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.11 Incidence of adverse reactions by dose of MTX per body surface area"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (status of concomitant drug: MTX, status of MTX: details) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.12 Incidence of adverse reactions by history of treatment with biological products"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (status of previous medication: biological products) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.13 Incidence of adverse reactions in children and non-children"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated for children (aged <15 years) and non-children (aged ≥15 years) as shown below. The number of patients analyzed, the number and percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions.

Number of adverse reactions: Number of adverse reactions that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.14 Frequency of serious adverse reactions"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Of adverse reactions during the safety analysis period, serious adverse reactions will be aggregated in accordance with "11. Data-layer separation" (timing of onset of adverse events) as shown below. The number of patients analyzed, the number and percentage of patients who experienced serious adverse reactions, the number of serious adverse reactions, the number of patients who experienced serious adverse reactions by type of serious adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients analyzed: Number of patients receiving treatment by period.

Number of patients who experienced serious adverse reactions: Number of patients who experienced serious adverse reactions during the administration period. When a single patient experienced multiple episodes of the same serious adverse reaction (PT), the event that occurred at the earliest time should be counted as one case.

Number of serious adverse reactions: Number of serious adverse reactions that occurred during the administration period. When a single patient experienced multiple episodes of the same serious adverse reaction (PT), the event that occurred at the earliest time should be counted as one case.

Types of serious adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same serious adverse reaction (PT), the event that occurred at the earliest time should be counted as one case.

Note: The version of MedDRA/J used should be provided.

"Table 2.15 Frequency of adverse reactions"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse reactions during the safety analysis period will be aggregated in accordance with "11. Data-layer separation" (timing of onset of adverse events) as shown below. The number of patients analyzed, the number and

percentage of patients who experienced adverse reactions, the number of adverse reactions, the number of patients who experienced adverse reactions by type of adverse reaction (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients analyzed: Number of patients receiving treatment by period.

Number of patients who experienced adverse reactions: Number of patients who experienced adverse reactions during the administration period. When a single patient experienced multiple episodes of the same adverse reaction (PT), the event that occurred at the earliest time should be counted as one case.

Number of adverse reactions: Number of adverse reactions that occurred during the administration period. When the same adverse reaction (PT) occurs multiple times in the same case, the event that occurred at the earliest time is counted as one case.

Types of adverse reactions: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When the same adverse reaction (PT) occurs multiple times in the same case, the event that occurred at the earliest time is counted as one case.

Note: The version of MedDRA/J used should be provided.

"Table 2.16.1 List of adverse events that occurred during and after treatment"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse events during the safety analysis period will be aggregated for the entire population, patients ongoingly treated at Week 24 of treatment, and discontinued patients (during treatment, after treatment, overall) as shown below.

During treatment: Adverse events that occurred after the start date of Humira treatment by the end date or the date of discontinuation of Humira treatment

After treatment: Adverse events that occurred after the end date or the date of discontinuation of Humira treatment by the start date of Humira treatment + 196 days

Number of adverse events: Number of adverse events that occurred. When a single patient experienced multiple episodes of the same adverse event (PT) during and after the administration, they should be counted as one event.

Types of adverse events: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse event (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

"Table 2.16.2 List of serious adverse events that occurred during and after treatment"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Of adverse events during the safety analysis period and adverse events outside the safety analysis period, serious adverse events will be aggregated for the entire population, patients ongoingly treated at Week 24 of treatment, and discontinued patients (during treatment, after treatment, overall) as shown below.

During treatment: Adverse events that occurred after the start date of Humira treatment by the end date or the date of discontinuation of Humira treatment

After treatment: Adverse events that occurred after the end date or the date of discontinuation of Humira treatment by the start date of Humira treatment + 196 days

Number of serious adverse events: Number of serious adverse events that occurred. When a single patient experienced multiple episodes of the same serious adverse event (PT) during and after the administration, they should be counted as one event.

Types of serious adverse events: Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same serious adverse event (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.

13.3. Efficacy

"Table 3.1 DAS28 remission rates by background factor"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28-4/ESR, the number of patients who remitted and the remission rate will be calculated in accordance with "11. Data-layer separation" (age 1, age 2, age 3, sex, body weight, BMI, reason for use and type of disease, disease duration 2, complications, complication: liver disorder, complication: renal disorder, complication: cardiovascular disorder, complication: blood disorder, complication: respiratory disorder, complication: other, past medical history, history of allergy, Steinbrocker Staging System, Steinbrocker Functional Classification, administration method category, previous medications, status of previous medication: biological product, status of previous medication: MTX, status of previous medication: corticosteroid, status of previous medication: NSAIDs, status of previous medication: Other DMARDs, concomitant drugs, status of concomitant drug: MTX, status of MTX: details, status of concomitant drug: corticosteroid, status of concomitant drug: NSAIDs, status of concomitant drug: Other DMARDs).

For the remission rates, Fisher's exact test should be conducted when the

background factor is a nominal scale and Mann-Whitney U test should be conducted when the background factor is an ordinal scale.

Notes: • Reason for use and type of disease may be redundantly aggregated. No test will be conducted for this item.

"Table 3.2.1 Remission rates in patients switched to other biological products"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28-4/ESR, the number of patients, the number of patients remitted and the remission rate will be calculated on the basis of the number of patients switched to other biological products and the breakdown of the reasons for switching (remission, subtherapeutic response, onset of adverse events, patient's request, no hospital visit [including hospital transfer], other).

Notes: • The breakdown of the reasons for switching may be redundantly aggregated.
• "Onset of an adverse event" should apply only when "Onset of an adverse event" is selected and an adverse event during safety analysis period has occurred.

"Table 3.2.2 Remission rates in combination therapy for juvenile idiopathic arthritis"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28-4/ESR, the number of patients, the number of patients remitted and the remission rate will be calculated on the basis of combination therapy for juvenile idiopathic arthritis (no, yes, unknown/unspecified). For patients receiving combination therapy, the number of patients, the number of patients remitted and the remission rate by breakdown of combination therapy (rehabilitation, other, unknown) will be calculated.

Notes: The breakdown of combination therapy may be redundantly aggregated.

"Table 3.2.3 Remission rates by duration of combination use of MTX for juvenile idiopathic arthritis"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28-4/ESR, the number of patients remitted and the remission rate will be calculated on the basis of combination use of MTX for juvenile idiopathic arthritis (no, yes, unknown/unspecified). Where there is a duration of combination use of MTX, the number of patients, the number of patients remitted and the remission rate by breakdown of duration of combination use (after the start of Humira treatment up to the end date of Humira treatment, at least a dose used during Humira treatment, unknown/unspecified) will be calculated.

Notes: The breakdown of duration of combination use may be redundantly aggregated.

"Table 3.3 Changes in anti-CCP antibodies"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For anti-CCP antibodies, the basic statistics of values measured before the start

of treatment and at 24 weeks after the start of treatment will be calculated in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Basic statistics will also be calculated for the amount of change from before the start of treatment, and a paired t-test will be conducted.

Note: None in particular.

"Table 3.4.1 Changes in DAS 28-4/ESR"

Analysis object: Patients included in the efficacy analysis set (DAS28-4/ESR)

Purpose of analysis: For DAS28-4/ESR, the basic statistics of values measured before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment will be calculated in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Basic statistics will also be calculated for the amount of change from before the start of treatment, and a paired t-test will be conducted.

Note: None in particular.

"Table 3.4.2 Changes in DAS28-4/CRP"

Analysis object: Efficacy analysis set (DAS28-4/CRP)

Purpose of analysis: For DAS28-4/CRP, the basic statistics of values measured before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment will be calculated in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Basic statistics will also be calculated for the amount of change from before the start of treatment, and a paired t-test will be conducted.

Note: None in particular.

"Table 3.5.1 Changes in EULAR response"

Analysis object: Patients included in the efficacy analysis set (DAS28-4/ESR)

Purpose of analysis: For improvement in DAS28-4/ESR assessed by EULAR Response Criteria, the number and percentage of patients will be calculated on the basis of improvement in DAS28-4/ESR at 4, 8, 12, 16 and 24 weeks after the start of treatment and at the final assessment in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Furthermore, the number of patients showing efficacy and the efficacy rate of improvement in DAS28-4/ESR as well as its 95% confidence interval will be calculated.

Note: None in particular.

"Table 3.5.2 Efficacy rates assessed by EULAR Response Criteria by background factor"

Analysis object: Patients included in the efficacy analysis set (DAS28-4/ESR)

Purpose of analysis: For improvement in DAS28-4/ESR assessed by EULAR Response Criteria at

the final assessment, the number of patients who showed efficacy and the efficacy rate will be calculated in accordance with “11. Data-layer separation” (age 1, age 2, age 3, sex, body weight, BMI, reason for use and type of disease, disease duration 2, complications, complication: liver disorder, complication: renal disorder, complication: cardiovascular disorder, complication: blood disorder, complication: respiratory disorder, complication: other, past medical history, history of allergy, Steinbrocker Staging System, Steinbrocker Functional Classification, administration method category, previous medications, status of previous medication: biological product, status of previous medication: MTX, status of previous medication: corticosteroid, status of previous medication: NSAIDs, status of previous medication: Other DMARDs, concomitant drugs, status of concomitant drug: MTX, status of MTX: details, status of concomitant drug: corticosteroid, status of concomitant drug: NSAIDs, status of concomitant drug: Other DMARDs).

For the efficacy rates, Fisher's exact test should be conducted when the background factor is a nominal scale and Mann-Whitney U test should be conducted when the background factor is an ordinal scale.

Notes: ・ Reason for use and type of disease may be redundantly aggregated. No test will be conducted for this item.

“Table 3.5.3 Remission rates assessed by DAS28-4/ESR by reason for use and type of disease”

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28 disease activity, the number and percentage of patients will be calculated on the basis of DAS28 disease activity before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment in accordance with “11. Data-layer separation” (reason for use and type of disease” and “12. Handling of data on tests/timing of assessment” (time window for efficacy assessment). The 95% confidence interval of the remission rates will also be calculated.

Notes: Patients with more than one reason for use and type of disease will be redundantly aggregated for each type of disease.

As the analysis object is patients included in the efficacy analysis set, oligoarthritis (persistent) will be excluded.

“Figure 3.5.3.1 Remission rates assessed by DAS28-4/ESR by reason for use and type of disease (overall)”

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28 disease activity in relation to reason for use and type of disease (overall), a bar graph will be created for DAS28 disease activity before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment in accordance with “11. Data-layer separation” (reason for use and type of disease” and “12. Handling of data on tests/timing of

assessment" (time window for efficacy assessment).

Note: None in particular.

"Figure 3.5.3.2 Remission rates assessed by DAS28-4/ESR by reason for use and type of disease (generalised arthritis)"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28 disease activity in patients whose reason for use and type of disease is generalised arthritis, a bar graph will be created for DAS28 disease activity before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment in accordance with "11. Data-layer separation" (reason for use and type of disease" and "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). A bar graph will also be created on the basis of reason for use and type of disease.

Note: None in particular.

"Figure 3.5.3.3 Remission rates assessed by DAS28-4/ESR by reason for use and type of disease (oligoarthritis [extended])"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28 disease activity in patients whose reason for use and type of disease is oligoarthritis (extended), a bar graph will be created for DAS28 disease activity before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment in accordance with "11. Data-layer separation" (reason for use and type of disease" and "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment).

Note: None in particular.

"Figure 3.5.3.4 Remission rates assessed by DAS28-4/ESR by reason for use and type of disease (polyarthritis [RF negative])"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28 disease activity in patients whose reason for use and type of disease is polyarthritis (RF negative), a bar graph will be created for DAS28 disease activity before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment in accordance with "11. Data-layer separation" (reason for use and type of disease" and "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment).

Note: None in particular.

"Figure 3.5.3.5 Remission rates assessed by DAS28-4/ESR by reason for use and type of disease (polyarthritis [RF positive])"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For DAS28 disease activity in patients whose reason for use and type of disease is polyarthritis (RF positive), a bar graph will be created for DAS28

disease activity before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment in accordance with "11. Data-layer separation" (reason for use and type of disease" and "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment).

Note: None in particular.

"Table 3.6.1 Changes in CDAI"

Analysis object: Patients included in the efficacy analysis set (CDAI)

Purpose of analysis: For CDAI, the basic statistics of values measured before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment will be calculated in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Basic statistics will also be calculated for the amount of change from before the start of treatment, and a paired t-test will be conducted.

Note: None in particular.

"Table 3.6.2 Changes in SDAI"

Analysis object: Patients included in the efficacy analysis set (SDAI)

Purpose of analysis: For SDAI, the basic statistics of values measured before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment will be calculated in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Basic statistics will also be calculated for the amount of change from before the start of treatment, and a paired t-test will be conducted.

Note: None in particular.

"Table 3.7 Trends in other efficacy endpoints"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: For tender joint count, swollen joint count, VAS assessed by the patient, VAS assessed by a doctor, ESR, CRP, serum MMP-3 concentration, height and weight, the basic statistics of values measured before the start of treatment, at 4, 8, 12, 16 and 24 weeks after the start of treatment, and at the final assessment will be calculated in accordance with "12. Handling of data on tests/timing of assessment" (time window for efficacy assessment). Basic statistics will also be calculated for the amount of change from before the start of treatment, and a paired t-test will be conducted.

Note: None in particular.

"Table 4.1 List of patients excluded from the safety analysis set and patients excluded from the efficacy analysis set of special drug use-results surveys, etc. (including reasons for exclusion)"

Analysis object: Patients excluded from the safety analysis set, patients excluded from the efficacy analysis set

Purpose of analysis: A list of case numbers for patients excluded from the safety analysis set and patients excluded from the efficacy analysis set, and patients for whom the reason for exclusion was output will be created.

Note: Where one patient has more than one reason for exclusion, they should be linked with commas when output.

"Table 4.2 List of patients"

Analysis object: Patients with fixed CRFs

Purpose of analysis: A list of patients analyzed will be created for the following items:
Case number, sex, age, body weight, disease duration, reason for use and type of disease, adverse event (disease name [MedDRA PT]), onset date, outcome, seriousness, causal relationship, status of adverse event), status of adverse reaction, MedDRA (SOC code, System Organ Class, PT code), adverse event term provided by a doctor, date of outcome, status of Humira treatment (start date of treatment, end date of treatment, days of treatment, initial dose, maximum dose, reason for discontinuation, status of treatment after discontinuation), status of complications, status of past medical history, hepatitis B virus tests (HBs antigen, HBs antibody,HBc antibody), tuberculosis tests (tuberculin skin test, Quantiferon test, chest x-ray, chest CT), efficacy (DAS28-4/ESR, DAS28-4/ESR [figure rounded down to the second decimal place], effective, ineffective) efficacy at discontinuation of treatment (DAS28-4/ESR, DAS28-4/ESR [figure rounded down to the second decimal place] effective/ineffective), flag identifier (patients included in the safety analysis set, patients included in the efficacy analysis set, adverse events outside the survey period, excluded adverse events, deaths, children, the elderly, pregnant and parturient women, liver disorder, renal disorder, patients infected with hepatitis B virus, patients with 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 congestive cardiac failure, patients with interstitial pneumonia, patients who received live vaccine), information on follow-up CRFs (with or without onset of malignant tumour [at 1 year], with or without onset of malignant tumour [at 2 years], disease name [diagnosis], onset date [date of diagnosis]).

Note: Where one patient has more than one reason for use and type of disease, they should be linked with commas when output.

- For efficacy at discontinuation of treatment (DAS28-4/ESR, effectiveness/ineffective), "-" (not applicable) should be output for patients other than discontinued patients.
- For flag identifiers, "○" (applicable) or "-" (not applicable) should be output.

"Table 4.3 List of status of Humira treatment"

Analysis object: Patients with fixed CRFs

Purpose of analysis: A list of summary of patients analyzed will be created for the following items: Case number, administration method category (at the start of treatment, during treatment), consultation category at the start of treatment, dose (dose at the start of treatment, maximum dose, dosing intervals), number of daily doses (maximum), change in treatment status, administration period (start date of treatment, end date of treatment), discontinuation of treatment (yes/no, reason for discontinuation, drug name after switching), flag identifiers (patients included in the safety analysis set, patients included in the efficacy analysis set, patients deviated from recommended dosage and administration of Humira, patients who received an increased dose).

Note: For flag identifiers, "◯" (applicable) or "-" (not applicable) should be output.

"Table 4.3.2 List of patients in whom a dose of Humira was changed"

Analysis object: Patients with fixed CRFs

Purpose of analysis: A list of summary of patients analyzed will be created for the following items: Case number, administration method category, consultation category, body weight, dose, administration period (start date of treatment, end date of treatment), reason for the change in dose, discontinuation of treatment (yes/no, reason for discontinuation).

Note: Multiple rows per patient should be output so that dose increase/reduction can be seen.

"Table 4.3.3 List of status of treatment with previous medications"

Analysis object: Patients with fixed CRFs

Purpose of analysis: A list of summary of patients analyzed will be created for the following items: Case number, drug category, drug name, route of administration, administration period (start date of treatment, end date of treatment), status of Humira treatment (start date of treatment, end date of treatment), flag identifier (patients included in the safety analysis set, patients included in the efficacy analysis set).

Notes:
- Patients with previous medications should be output.
- For flag identifiers, "◯" (applicable) or "-" (not applicable) should be output.

"Table 4.3.4 List of concomitant drugs and concomitant therapies"

Analysis object: Patients with fixed CRFs

Purpose of analysis: A list of summary of patients analyzed will be created for the following items: Case number, drug name, route of administration, administration period (start date of treatment, end date of treatment), status of Humira treatment (start date of treatment, end date of treatment), combination therapy, status of adverse events, status of adverse reactions, efficacy (DAS28-4/ESR, effective/ineffective), flag identifier (patients included in the safety analysis set, patients included in the efficacy analysis set).

Notes:
- Patients with concomitant drugs should be output.

・ For flag identifiers, "◯" (applicable) or "-" (not applicable) should be output.

"Table 4.4 List of summaries of patients analyzed (Appended Form 3)"

Analysis object: Patients with fixed CRFs

Purpose of analysis: A list of summary of patients analyzed will be created in accordance with the following definitions:

(1) Case number: Output a sequential number for each patient starting from 1.

(2) Facility name (company code): Output the facility name in Japanese from "External file for provision of analysis" containing facility names.

(3) Type/code of establishment: Output the code from "External file for provision of analysis" containing types/codes of establishment.

(4) Name of prefecture (location): Output the name of the prefecture from "External file for provision of analysis" containing names of prefectures.

(5) Abbreviated name of patient: Since this is not collected in the CRF, this should be output as "not applicable".

(6) Sex: Output the sex (male, female, unknown, unspecified) provided in the CRF in Japanese.

(7) Date of Birth (or age): As described in "Guidance for application for reexamination", output the age described in the CRF as "A + age (XX) + 0000'". (XX should be replaced by age)

(8) Inpatient/outpatient: Output the consultation category (inpatient, outpatient, unknown, unspecified) at the initial dosing of Humira provided in the CRF.

(9) Reason for use (disease code, disease name): If the reason for use and type of disease provided in the CRF is "other", output the MedDRA/J LLT code and LLT term, respectively. Leave the disease code blank if other than "other", and output the reason for use and type of disease provided in the CRF only to disease name as it is.

(10) Severity before the start of treatment: Output the Steinbrocker Functional Classification (Class I, Class II, Class III, Class IV) provided in the CRF. If unknown or not provided, output it as "unknown".

(11) Complications (status, number provided, name):

・ Status: Output "status of complications" defined in "10.1 General".

・ Number provided: This should be the number of PT codes for complications coded with MedDRA/J. The same PT codes in a single patient should be considered as one case. Where there is no complication, this should be "0".

・ Name: This should be PT terms for complications coded with MedDRA/J. Detailed categories of complications, disease names of complications, and sequential numbers of complications should be arranged in the sequential order for each patient. Leave this blank when the number of cases provided is "0". Output data should be in the order of MedDRA/J PT code, sequential number, and description in the CRF.

(12) Route of administration: Output "SC".

(13) Maximum dose (per dose): This should be the maximum amount per dose. From doses described in the CRF, the maximum dose should be output for each patient.

(14) Mean dose (per dose): This should be the average amount per dose. From "treatment status (total number of doses, total dose)" defined in "10.1 General", values of "total dose/total

number of doses" should be output.

(15) Unit: Output "MG".

(16) Number of daily doses (maximum): Where there is no patient receiving two or more doses per day, "1" should be output.

(17) Duration of use: From "treatment status (total number of doses, total dose)" defined in "10.1 General", a value of "total number of doses" should be output.

(18) Concomitant drugs (drug code, representative drug name, number provided):

- Drug code, representative drug name: List these in the order of "concomitant drugs for juvenile idiopathic arthritis", "other concomitant drugs" with sequential numbers, and the concomitant drug listed on the top should be analyzed. Where there is no concomitant drug, the drug code should be blank and the representative drug name should be "none".
- Number provided: Count the drug codes rearranged above. Where there is more than one same code for a single patient, they should be counted as one. Where there is no concomitant drug, this should be "0".

(19) Degree of effect: Output DAS28-4/ESR (remission, non-remission) at the final assessment. Output "unspecified" if "clinical course" after the start of treatment is unspecified in the CRF, and "unknown" if indeterminable.

(20) Adverse reactions (organ name code, adverse reaction code, adverse reaction term, status, number provided): For adverse reactions during the safety analysis period described in the CRF, events with the same PT codes in a single patient should be counted as one record. They should be output in the order of onset date of adverse reactions, the order of international agreements, and the order of PT codes.

- Organ name code: This should be MedDRA/J SOC code. Leave this blank if the status is "no".
- Adverse reaction code: This should be MedDRA/J PT code. Leave this blank if the status is "no".
- ·Adverse reaction term: This should be PT term corresponding to MedDRA/J PT code. Leave this blank if the status is "no".
- Status: For adverse reactions during the safety analysis period, data with adverse events with undeniable causal relationship to Humira should be handled as "yes". If the status of adverse event is unknown, this should be handled as "unknown". If the status of adverse event has not been provided, this should be handled as "unspecified". Others should be handled as "no". Cases where the reason for patients excluded from the safety analysis set is "unevaluable" should be handled as "unknown".
- Number of provided: Count the number of PT codes. The same PT codes in a single patient should be considered as one case. Leave this blank if the status is "no".

(21) Outcome: For the PT codes output for adverse reactions, the top-priority outcome in the preference order of "outcome" defined in "10.2 Safety analysis" should be analyzed. Leave this blank where the status of adverse reactions is "no".

(22) CRF number: Output the CRF number.

(23) Dropouts: Patients excluded from safety should be output as "(drop out of both)" and patients included in safety and excluded from efficacy should be output as "(drop out of

efficacy)".

Note: The version of MedDRA/J used should be provided.

"Table 5.1 Incidence of malignant tumour"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: The number and percentage of patients will be aggregated for the status of malignant tumour (no, yes, unknown) by follow-up CRF (at 1 year, 2 years).

Note: None in particular.

"Table 6.1 Frequency of adverse events by seriousness"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: Adverse events will be aggregated by seriousness as shown below. The number of patients analyzed, the number of patients who experienced adverse events and the number of adverse events, the percentage of adverse events, the number of patients who experienced adverse events by type of adverse event (by SOC and PT) and their percentages against the patients analyzed will be calculated.

Number of patients who experienced adverse events (or serious adverse events): Number of patients who experienced adverse events (or serious adverse events).

Number adverse events (or serious adverse events): Number of adverse events (or serious adverse events) that occurred. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Incidence rates of adverse events (or serious adverse events) (%): Number of patients who experienced adverse events (or serious adverse events) ÷ patients included in the safety analysis set x 100.

Types of adverse events (serious adverse events): Should be calculated by SOC and by PT. Output data should be sorted in the order of international agreements and in the ascending PT code order. When a single patient experienced multiple episodes of the same adverse reaction (PT), they should be counted as one event.

Note: The version of MedDRA/J used should be provided.