Humira® For Subcutaneous Use

Special Drug Use-Results Survey

- Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice -

(Combo study; Adalimumab with high dose MTX)

Statistical Analysis Plan

Version 6.00

Date of preparation: April 9, 2018

Approval

Sponsor

Name of company	AbbVie GK	
Approver	Supervisor of post-marketing surveys, etc.	Signature
Date of approval	MM DD, YYYY	
Approver	General Manager of Medical Headquarters	Signature
Date of approval	MM DD, YYYY	
Approver	Safety management supervisor	Signature
Date of approval	MM DD, YYYY	
Approver	Physician who designed research plan	Signature
Date of approval	MM DD, YYYY	
Approver	Director of statistical analysis	Signature
Date of approval	MM DD, YYYY	

Contractor

Name of company	EPS Corporation	
Approver	Person responsible for statistical analysis operations	Signature
Date of approval	MM DD, YYYY	

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1. History of preparation/revision

Version number	Date of preparation/revision	Prepared/Revised by	Reason
1.00	8/5/2014	[redacted]	First version
1.10	2/17/2015		Review at each periodic safety report
2.00	2/15/2016		Changes in overall description methods Review of figures/tables and definitions in association in response to periodic safety report
3.00	3/15/2016		Review of figures/tables and definitions in response to reexamination
4.00	7/22/2016		Addition of figures/tables and definitions in response to periodic safety report
5.00	9/15/2017		Addition of figures/tables and definitions for the final analysis
6.00	4/9/2018		Addition of tables as adjustments prior to the implementation of the final analysis

2. Definition of terms and abbreviations

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

Terms and abbreviations	Definitions
Adverse event	An adverse event (AE) refers to any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease occurred in patients, whether or not considered related to the drug used.
Adverse reaction	Adverse events for which a causal relationship with Humira cannot be ruled out were handled as adverse reactions (ADRs).
Summary statistics	Summary statistics include the number of patients, mean, standard deviation, minimum, median, maximum.
MedDRA/J	Medical Dictionary for Regulatory Activities / Japanese edition
SOC	MedDRA/J System Organ Class
PT	MedDRA/J Preferred Term
LLT	MedDRA/J Lower Level Term
ACR	American College of Rheumatology
CDAI	Clinical Disease Activity Index

Terms and abbreviations	Definitions
CRP	C-Reactive Protein
DMARDs	Disease Modifying Antirheumatic Drugs
DAS	Disease Activity Score
EQ-5D	EuroQol Questionnaire 5 Dimensions
EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate
HAQ	Health Assessment Questionnaire
TSS	Total Sharp Score
mTSS	modified Total Sharp Score
MTX	Methotrexate
RA	Rheumatoid Arthritis
SDAI	Simplified Disease Activity Index
VAS	Visual Analog Scale
Children	Patients aged < 15 years
Adults	Patients aged between ≥ 15 years and < 65 years
Elderly	Patients aged ≥ 65 years

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 predetermine the matters related to statistical analysis operation conducted in accordance with the protocol of the "Special Drug Use-Results Survey on Humira® For Subcutaneous Use 40 mg syringe 0.8 mL - Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice -" (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 in order to understand safety and efficacy in concomitant therapy with high dose (≥ 12mg/week) methotrexate (hereafter, referred to as "MTX") in Japanese patients with rheumatoid arthritis (hereafter, referred to as "RA") under the actual clinical conditions as a special drug use-results survey on Humira® For Subcutaneous Use 40 mg syringe 0.8 mL (nonproprietary name: Adalimumab) (hereafter, referred to as "Humira").

4.2. Survey plan

(1) Survey subjects

Japanese RA patients who receive Humira meeting the following conditions.

1) Patients with the duration of RA within 2 years from the diagnosis at the start of Humira treatment
2) Patients receiving MTX for 3 months or longer at the start of Humira treatment
3) Patients receiving more than 12 mg/week of MTX at the start of Humira treatment
4) Patients with DAS28 (CRP) > 3.2 at the start of Humira treatment (4 weeks prior to treatment start - start date of treatment)

(2) Patients excluded from the survey

1) Patients who have received biological products

4.3. Planned sample size

(1) Planned number of patients surveyed

350 patients

(2) Rationale for setting

The patient with Disease Activity Score 28 (hereafter, referred to as "DAS28") below 2.6 at week 52 was estimated to be 55% (the expected observation was 55% and the estimated difference was 12.3% for the literature data 42.7%), and the number of patients required to detect at a 5% level of significance level (paired) and a 90% power was calculated to be 171 patients. As the number needed to treat to secure this number of patients, the dropout rate at week 52 in this survey was assumed to be 50% based on the dropout rate of approximately 32% at week 24 in the all-case surveillance with Humira, and the planned number of patients surveyed was calculated to be 350 patients.

5. Items to be evaluated in analysis and examining method

(1) Analysis items

1) Matters concerning patient composition
    1) Number of patients with returned CRFs
    2) Number of patients included in the safety analysis set
    3) Number of patients included in the efficacy analysis set

2) Matters concerning safety
   1) List of incidences of ADRs/infections
   2) Factors considered to have an influence on safety
      Incidence of ADRs by patient background factor, etc.
   3) AEs occurred during or after treatment
      List of incidences of serious AEs, etc.
3) Matters concerning efficacy
   1) DAS28 response, trend, percentage of remission, etc.
   2) CDAI response, trend, percentage of remission, etc.
   3) SDAI response, trend, percentage of remission, etc.
   4) Trends in HAQ, etc.
   5) Trends in EQ-5D, etc.
   6) Trends in mTSS/bone erosion score/joint space narrowing score and the percentage of patients without worsening of mTSS/bone erosion score/joint space narrowing score (change from the survey start < 0 and < 0.5), etc.
   7) Factors considered to have an influence on efficacy (list of efficacy by patient background factor, etc.)

(2) Analysis methods
Appropriate methods including χ^2 test according to the scale and nature of the analysis data should be used.

6. Schedule of the analysis

Purpose of the analysis	Survey unit period and time frame for reexamination
The 11th Periodic Safety Report	December 31, 2012 - June 30, 2013
The 12th Periodic Safety Report	July 1, 2013 - December 31, 2013
The 13th Periodic Safety Report	January 1, 2014 - June 30, 2014
The 14th Periodic Safety Report	July 1, 2014 - December 31, 2014
The 15th Periodic Safety Report	January 1, 2015 - December 31, 2015
The 16th Periodic Safety Report	January 1, 2016 - April 15, 2016
Application for reexamination	April 16, 2008 - April 15, 2016
Final Analysis	April 16, 2008 - July 31, 2018 (planned)

*Since there is no unit period for the final analysis, the proposed date for the final report is considered as the completion date.

7. Software/dictionaries used for analysis

7.1. Statistical analysis and tabulation software

The software and versions used for analyses are shown below.

	Software and versions
OS	Microsoft Windows 7 or a higher version should be used.
Statistical analysis software	SAS Ver. 9.2 or a higher version should be used.
Tabulation software	Microsoft Excel 2007 or a higher version should be used.

7.2. Dictionaries used

The dictionaries used for names of AEs and complications, and names of drugs are shown below.

Item	Names and versions of dictionaries	Remark
Types of AE and ADR/infection	Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) *An appropriate version should be used for aggregation according to the timing of analysis.	・AEs and ADRs/infections should be classified into System Organ Class (SOC), and appropriate terms should be selected from the Preferred Terms (PT) and described. ・ If indicating SOC, it should be indicated in accordance with the order of the international agreement.
Drug names (concomitant drugs)	Prescription drug name data file *An appropriate version is used for tabulation according to the time of analysis.	・ When tabulating by concomitant drug name, nonproprietary names (seven-digit codes) should be used in principle; however, if there is no seven-digit code, therapeutic categories (the code with the highest digit among the available one-digit code, two-digit code, three-digit code or four-digit code) should be used where necessary.

8. Definitions of populations used for analysis

Name of population	Definitions
Patients enrolled	Patients who were confirmed to be enrolled.
Patients with returned CRFs	Patients whose CRFs are collected.
Patients with fixed CRFs	Patients whose CRFs are fixed.
Patients excluded from the safety analysis set	Patients meeting any of the conditions for excluding from safety analysis. Refer to the description in the "handling criteria of patients" of this survey for the conditions for exclusion from the safety analysis set.
Patients included in the safety analysis set	Patients with fixed CRFs except for the patients excluded from the safety analysis set
Patients excluded from the efficacy analysis set	Patients meeting any of the conditions for excluding from efficacy analysis. Refer to the description in the "handling criteria of patients" of this survey for the conditions for exclusion from the efficacy analysis set.
Patients included in the efficacy analysis set (DAS28-4CRP, DAS28-4ESR, CDAI, SDAI, HAQ-DI, EQ-5D,)	Patients included in the safety analysis set except for the patients excluded from the efficacy analysis set Among the patients included in the efficacy analysis set, the patients included in the efficacy analysis set according to each efficacy endpoint other than DAS28-4CRP indicated in the left should also be established.
Patients included in the efficacy analysis set (mTSS 52 weeks)	Among the patients included in the efficacy analysis set, patients whom mTSS was evaluated at week 52 reading session score.
Patients included in the efficacy analysis set (mTSS at week 104)	Among the patients included in the efficacy analysis set, patients whom mTSS was evaluated at week 104 reading session score.
Patients included in the efficacy analysis set (third CRF) (DAS28-4CRP, DAS28-4ESR, CDAI, SDAI, HAQ-DI,EQ-5D, mTSS)	(1) Patients included in the efficacy analysis set with the fixed third CRF. (2) Patients whom the final Humira treatment is later than week 52 + 4 weeks or later. (3) Patients with DAS28-4CRP measurement within the evaluation range from baseline and week 52 and after the lowest limit date within the evaluation range of week 76. Patients meeting three of the above conditions should be the patients included in the efficacy analysis set (third CRF). In addition, among the patients included in the

Name of population	Definitions
	efficacy analysis set (third CRF), patients with the measurements of the endpoints other than DAS28-4CRP and mTSS conducted at three time points: baseline, evaluation range of week 52, and after the latest limit date within the evaluation range of week 76 should be handled as the patients evaluated in the third CRF. In mTSS, patients with the measurements of X ray score obtained at the second reading session conducted at three points: baseline, within the evaluation range of week 52, and after the latest limit date of the evaluation range of week 76 should be handled as patients evaluated in the third CRF among the patients included in the efficacy analysis set (third CRF) and patients included in the efficacy analysis set (mTSS at week 104). Refer to "12. Handling of data on tests/evaluation time" for the range of evaluation time. The patients included in the efficacy analysis set by each efficacy endpoint other than DAS28-4CRP indicated in the left should also be established.

9. General agreements concerning analysis

9.1. Handling of missing data

Missing data should not be complemented in the analysis.

9.2. Handling of incomplete dates

Missing dates should be treated as "undescribed". 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. 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
Quantitative data	Number of patients, mean, standard deviation (SD), median, minimum, maximum, etc.

9.4. Number of digits shown

The number of digits expressed is as follow.

Numeric type	Number of digits expressed
Mean, SD, median, 95% confidence interval (CI)	The figures should be rounded to +2 significant digits of the data, and expressed to +1 significant digit.
Minimum, maximum	Figures should be displayed with the same number of digits as the displayed digits of the data.
Number of patients	The figures should be expressed in integer values.
Percentage, rate	The incidence of AEs (including ADRs) should be rounded to the second decimal place and expressed to two decimal places. Those other than the incidence of AEs (including ADRs) should be rounded to the first decimal place and expressed to one decimal place.
p value	The figures should be rounded off to the fourth decimal place and expressed to four decimal places. However, if the figure is smaller than 0.0001, it should be expressed as $p < 0.0001$ without exception.
Number of significant digits	1 [age, total number of Humira doses, period to completion of treatment (day), tender joint count, swollen joint count, ESR] 0.1 [duration of illness, duration of smoking, weight, MTX dose, DAS28-4ESR, DAS28-4CRP, CDAI, SDAI, VAS, HAQ, mTSS, bone erosion score, joint space narrowing score] 0.01 [CRP] 0.001 [EQ5D]

9.5. Numerical expression rule

Case	Expression rule
When figures are incalculable	Hyphen "-"

9.6. Level of significance

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

9.7. 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, the period should be determined upon consultation with the sponsor.

10. Data derivation and calculation methods

10.1. Overall

Name of data	Derivation and calculation methods
Age	The age on the start date of treatment should be calculated. However, if the birth date is unknown, the age described in the CRF should be used. Since it is obtained up to birth month and year in the CRF, the birth date should be the 1st of the month.
Number of survey institutions	It should be tabulated by institution code.
Number of patients surveyed	It should be tabulated by case (number).
Calculation of period	Period = the relevant date - the initial date +1
Definition of unit period	One week should be converted into seven days.
Date of initial Humira treatment	Of the start dates of treatment in Humira treatment status, the earliest date should be the date of initial Humira treatment.
Date of final Humira treatment	Of the completion dates of treatment in Humira treatment status, the latest date should be the date of final Humira treatment. However, the following measures should be taken according to the final record of each patient. ・For patients whose the start date of treatment exceeds the planned completion date of each CRF and the completion date of treatment is described as "continuing," the start date of treatment should be complemented to the complete date of treatment of the record. ・For patients whose the start date of treatment is prior to the planned completion date of each CRF and the completion date of treatment is described as "continuing," the completion date of treatment should be complemented to the complete date of treatment of each CRF. ・If the start date of treatment with a biological product and the final record of the completion date of Humira treatment are the same date in the third CRF, the completion date of Humira treatment should be -1 day and the overlap of the treatment period should be deleted. *Planned completion date of each CRF First CRF: start date of Humira treatment + 167 days Second CRF: start date of Humira treatment + 363 days Third CRF: start date of Humira treatment + 727 days
Period to treatment completion (day)	It should be between the date of initial Humira treatment and the date of final Humira treatment.

Name of data	Derivation and calculation methods
Treatment period (day) Completion date of treatment *Per record	It should be between the start date of Humira treatment and the completion date of treatment per treatment record. When the completion date of treatment in the information on the previous treatment within the same CRF and the start date of treatment in the information on the relevant treatment are the same date, the completion date of treatment in the information on the previous treatment should be - 1 day. The records with the dose of 0 mg should be excluded from the analysis.
Dosing intervals (day) *Per record	Biweekly should be 14 days, once in three weeks should be 21 days, and once in four weeks should be 28 days, respectively.
Total number of doses	The total after calculating the number of doses per record by rounding up the first decimal place should be taken for treatment period (day)/dosing intervals (day).
Patients who discontinued Humira treatment	If the final fixed CRF is the first or second CRF, the patients should be handled as the patients with a description in the "treatment discontinuation" column in the final CRF. If the final fixed CRF is the third CRF, the patient should be handled as the patients with a description of the completion date of treatment in the final record of the "Humira treatment status" column in the final CRF.
Patients who are continuing Humira treatment	If the final fixed CRF is the first or second CRF, the patients should be handled as the patients without a description in the "treatment discontinuation" column in the final CRF. If the final fixed CRF is the third CRF, the patient should be handled as the patients with a description of "continuing" in the final record of the "Humira treatment status" column in the final CRF.
Date of treatment discontinuation	In patients who discontinued Humira treatment, the completion date of Humira treatment should be the date of discontinuation.
Low body weight	Patients with body weight of < 30 kg.
Date of survey discontinuation	It should be the date of survey discontinuation described in the third CRF. It should be the start date of treatment with other biological products, or the older date among the last follow-up date.
AE follow-up period	It should be between the date of initial Humira treatment and the date of initial Humira treatment + 755 days.
Presence of complications	When any of the details of the complication is evaluated as present, it should be handled as "present," when it is described as no complication, it should be handled as "absent," and when there is no description both in complication and the details, it should be handled as "undescribed."

Name of data	Derivation and calculation methods
Presence of complication: liver disorders	Patients with the complication items applicable to the details of liver disorders (hepatitis, hepatitis virus carrier, hepatic cirrhosis, hepatic steatosis, others) should be handles as "present," when there is no description in the presence of complications, it should be handled as "undescribed," and others should be handled as "absent."
Presence of complication: renal disorders	Patients with the complication items applicable to the details of renal disorders (nephritis, renal failure, nephrotic syndrome, others) should be handles as "present," when there is no description in the presence of complications, it should be handled as "undescribed," and others should be handled as "absent."
Presence of complication: cardiovascular disorders	Patients with the complication items applicable to the details of cardiovascular disorders (cardiac failure, angina pectoris, arrhythmia, hypertension, others) should be handles as "present," when there is no description in the presence of complications, it should be handled as "undescribed," and others should be handled as "absent."
Presence of complication: blood disorders	Patients with the complication items applicable to the details of blood disorders (anaemia, aplastic anaemia, pancytopenia, others) should be handles as "present," when there is no description in the presence of complications, it should be handled as "undescribed," and others should be handled as "absent."
Presence of complication: respiratory disorders	Patients with the complication items applicable to the details of respiratory disorders [interstitial pneumonia, asthma, obstructive pulmonary disease, bronchitis bacterial, nontuberculous mycobacteriosis (including colonization), others] should be handles as "present," when there is no description in the presence of complications, it should be handled as "undescribed," and others should be handled as "absent."
Presence of complication: others	Patients with the complication items applicable to the details of blood disorders [diabetes mellitus, gastrointestinal disorder, osteoporosis, malignant tumour, demyelinating disorders, collagen disorders (other than rheumatoid arthritis), others] should be handles as "present," when there is no description in the presence of complications, it should be handled as "undescribed," respectively, and others should be handled as "absent."
Presence of a past history	When any of the details of the past history is evaluated as present, it should be handled as "present," when it is described as no complication, it should be handled as "absent," and when there is no description both in past history and the details, it should be handled as "undescribed."

Name of data	Derivation and calculation methods
Presence of a history of allergy	If there is nothing applicable to a history of allergy, it should be handled as "undescribed." In the details, if the patient is applicable to both "drugs" and "food," it should be handled as "both."
RA stage/progression	If there is no description in the RA stage/progression, it should be handles as "undescribed."
Disabilities in RA	If there is no description in the RA disability index, it should be handles as "undescribed."
Presence of concomitant drugs (At start date of Humira treatment)	If there is any drug administration on the date of initial Humira treatment, it should be handled as "present," and others should be handled as "absent."
Presence of concomitant drugs (During treatment with Humira)	If there is any drug administration during treatment with Humira, it should be handled as "present," and others should be handled as "absent." Administration during treatment with Humira refers to all administration cases not applicable to the followings. ・The completion date of treatment with a concomitant drug is prior to the date of initial Humira treatment ・The start date of treatment with a concomitant drug is after the date of final Humira treatment
Concomitant drug: MTX (mg/week)	The dose of MTX during the period including the date of initial Humira treatment should be sorted into the following three categories: "≥ 12.0 mg/week and < 14.0 mg/week," "≥ 14.0 mg/week and < 16.0 mg/week," and "≥ 16.0 mg/week."
Start date of MTX treatment *Per record	When there is more than one record of the same reason for use and same dose within the same patient and the treatment period is overlapped in these records, the information in the record in the latest CRF should be adopted and the start date of MTX treatment of the record should be used. The records with the dose of 0 mg should be excluded from the analysis.
Completion date of MTX treatment *Per record	When the completion date of treatment in the information on the previous treatment and the start date of treatment in the information on the relevant treatment are the same date within the same patient, the completion date of treatment in the information on the previous treatment should be - 1 day.
Treatment continuing group	Among the patients included in the efficacy analysis set (third CRF), patients who are continuously receiving Humira at week 104.

Name of data	Derivation and calculation methods
Treatment discontinued group	Among patients included in the efficacy analysis set (third CRF), patients whom the discontinuation date of Humira treatment and the relevant date at week 104 is ≥ 24 weeks apart of the patients continuing the survey who discontinued Humira treatment later than week 52. Or the patients whom the date of final follow-up (or the lower date of the start date of treatment with other biological product other than Humira) is ≥ 24 weeks apart from the date of Humira treatment discontinuation among the patients discontinued survey who discontinued Humira treatment later than week 52.
Survey discontinued group	Among the patients included in the efficacy analysis set (third CRF), the patients with the entry of the start date of treatment with other biological products other than Humira or the final follow-up date not applicable to the conditions for the treatment discontinued group.
Other groups	Among the patients included in the efficacy analysis set (third CRF), patients who are not applicable to the treatment continuing group, treatment discontinued group or survey discontinued group.
Mode of administration	All modes of administration during the Humira treatment period should be summarized, and indicated by five levels of category: administration by a physician only, administration by a physician to self-administration, self-administration only, self-administration to administration by a physician, and administration by a physician and self-administration alternatively. When tabulating, the patients should be categorized by "administration by a physician only" for patients who received Humira by administration by a physician only, "self-administration only" for patients with self-administration only, and "administration by a physician and self-administration" for patients received in both modes of administration and should be tabulated by group.
Dosage and administration	Dosage and administration should be indicated by the following four levels of categories: 40 mg/biweekly, 80 mg/biweekly, 40 mg/biweekly or 80 mg/biweekly, other .

10.2. Safety analysis

Name of data	Derivation and calculation methods
Adverse event	For adverse event-related data, "an AE matching list", the data set through the matching activities (matching of CRF data and safety information data), should be used. AEs with the same patient number should be aggravated and counted as one event when the PT is the same. However, when the novelty (known/unknown) is different within the same PT, such as in Appended Form 2, they should be tabulated separately.
Seriousness of AE	For seriousness of an AE aggravated from a single patient as the same PT, seriousness set through AE matching activities should be set in the following order of priority. Serious Non-serious
Causal relationship of AE	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 AE 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. Related Not related
Outcome of AE	Outcomes of AEs aggravated from a single patient as the same PT should be set in the following order of priority. Fatal Unknown Not recovered/Not resolved Recovered/Resolved with sequelae Recovering/Resolving Recovered/Resolved
Adverse reaction	AEs of which causal relationship is other than "not related" set through the AE matching activities are defined as ADRs.
Serious AEs	AEs of which seriousness set through the AE matching activities is "serious" are defined as serious AEs.
AEs outside the follow-up period	These should be handled as outside the safety analysis. AEs are defined that occurred prior to the start date of Humira treatment or at week 108 (treatment start date + 755).

10.3. Efficacy analysis

Name of data	Derivation and calculation methods
HAQ disability index	It should be calculated by the following formula. HAQ = ((A)+(B)+(C)+(D)+(E)+(F)+(G)+(H))/responded number of categories (A) Dressing and grooming (2 items in total) (B) Arising (2 items in total) (C) Eating (3 items in total) (D) Walking (2 items in total)

Name of data	Derivation and calculation methods
	(E) Hygiene (3 items in total) (F) Reach (2 items in total) (G) Grip (3 items in total) (H) Activity (3 items in total) At least 6 categories are required for calculation of HAQ. The highest score among the questions within the category should be adopted for the value of the categories from (A) through (H).
EQ-5D	The score should be calculated by means of "Japanese EQ-5D utility conversion table" <Reference 1> for the following items. (A) Mobility (B) Self-care (C) Usual activities (D) Pain/Discomfort (E) Anxiety/Depression <Reference 1> The Development Committee of the Japanese EuroQol Instrument (1998). 8.109-123. Journal of Health Care and Society
DAS28-4ESR	It should be calculated by the following formula. DAS28-4ESR=0.56×√(A)+0.28×√(B)+0.70×ln(C)+0.014×(D) (A) Number of 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) Global assessments of disease activity by the patient (VAS) (mm)
DAS28-4CRP	It should be calculated by the following formula. DAS28-4CRP=0.56×√(A)+0.28×√(B)+0.36×ln(((E)×10)+1)+0.014×(D)+0.96 Refer to (A), (B) and (D) DAS28-4ESR (E) C-reactive protein (CRP) (mg/dL)

<table>
<tr><th>Name of data</th><th>Derivation and calculation methods</th></tr>
<tr><td>EULAR judgement criteria for response</td><td>Both DAS28-4ESR and DAS28-4CRP should be evaluated in accordance with the following table.
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">EULAR DAS28 response</td></tr>
<tr><td>>1.2</td><td>0.6< ≤1.2</td><td>≤0.6</td></tr>
<tr><td rowspan="3">DAS28 at the evaluation time</td><td>≤3.2</td><td>Good response</td><td>Moderate response</td><td>No response</td></tr>
<tr><td>3.2< ≤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>
DAS28 response should be calculated from the EULAR DAS28 response (DAS28 of the origin) - (DAS28 at evaluation point).
Good Response, Moderate Response, or No Response should be judged based on the DAS28 and the response at the evaluation time.
Good Response and Moderate Response should be considered effective, and No Response as ineffective.</td></tr>
<tr><td>SDAI</td><td>It should be calculated by the following formula.
SDAI=(A)+(B)+(D)/10+(F)/10+(E)
Refer to (A), (B) and (D) DAS28-4ESR
(E) C-reactive protein (CRP) (mg/dL)
(F) Global assessments of disease activity by the physician (VAS) (mm)</td></tr>
<tr><td>CDAI</td><td>It should be calculated by the following formula.
CDAI=(A)+(B)+(D)/10+(F)/10
Refer to (A), (B) and (D) DAS28-4ESR
(F) Global assessments of disease activity by the physician (VAS) (mm)</td></tr>
<tr><td>Bone erosion score</td><td>Based on the reading session score table received from the sponsor, it should be calculated from the scores from two persons (or including the score by the third person) entered in the column of bone erosion.

Bone erosion score = the mean of the scores from two persons (when the score from the third person is obtained, two selected persons including the third person)</td></tr>
<tr><td>Joint space narrowing score</td><td>Based on the reading session score table received from the sponsor, it should be calculated from the scores from two persons (or including the score by the third person) entered in the column of JSN.

Joint space narrowing score = the mean of the scores from two persons (when the score from the third person is obtained, two selected persons including the third person)</td></tr>
<tr><td>mTSS</td><td>Based on the reading session score table received from the sponsor, it should be calculated from the scores from two persons (or including the score by the</td></tr>
</table>

Name of data	Derivation and calculation methods
	third person) entered in the column of total. mTSS = the mean of the scores from two persons (when the score from the third person is obtained, two selected persons including the third person)

11. Data-layer separation

<Patient background characteristics>

Data	Layer separation
Consultation category	Inpatient, outpatient, undescribed
Gender	Male, female, undescribed
Pregnancy/lactation (female)	Other than pregnant or lactating, pregnant, lactating, unknown, undescribed
Age (years)	Children (aged < 15 years), adults (aged ≥ 15 years and < 65 years), elderly (aged ≥ 65 years), undescribed
	(less than 15, 15 – 30, 30 – 50, 50 – 65, 65 – 75, 75 – 85, equal or more than 85, Unknown/Missing)*3
Weight (kg)	< 30, ≥ 30 and < 40, ≥ 40 and < 50, ≥ 50 and < 60, ≥ 60, unknown, undescribed
Duration of illness (month)	< 3, ≥ 3 and < 6, ≥ 6, unknown, undescribed
Complication	Present, absent, undescribed
Complication (liver disorder)	Hepatitis, hepatitis virus carrier, hepatic cirrhosis, hepatic steatosis, others
	(These should be tabulated by using categories of "without liver disorders," "with liver disorders," and "undescribed" in the table that is not requiring tabulation by the above disposition)
Complication: liver disorders (hepatitis)	Hepatitis B, other, undescribed
Complication: liver disorders (hepatitis virus carrier)	Hepatitis B,, others, undescribed
Complication: renal disorders	Nephritis, renal failure, nephrotic syndrome, others
	(These should be tabulated by using categories of "without renal disorders," "with renal disorders," and "undescribed" in the table that is not requiring tabulation by the above disposition)
Complication: cardiovascular disorders	Cardiac failure, angina pectoris, arrhythmia, hypertension, others
	(without cardiovascular disorders, with cardiovascular disorders, undescribed)
Complication: blood disorders	Anaemia, aplastic anaemia, pancytopenia, others

Data	Layer separation
	(These should be tabulated by using categories of "without blood disorders," "with blood disorders," and "undescribed" in the table that is not requiring tabulation by the above disposition)
Complication: respiratory disorders	Interstitial pneumonia, asthma, obstructive pulmonary disease, bronchitis bacterial, nontuberculous mycobacteriosis (including colonization), others (These should be tabulated by using categories of "without respiratory disorder," "with respiratory disorder," and "undescribed" in the table that is not requiring tabulation by the above disposition)
Complication: others	Diabetes mellitus, gastrointestinal disorder, osteoporosis, malignant tumour, demyelinating disorders, collagen disorders (other than rheumatoid arthritis), others
	(These should be tabulated by using categories of "without others," "with others," and "undescribed" in the table that is not requiring tabulation by the above disposition)
Past history	Present, absent, unknown, undescribed
Past history: details	Tuberculosis, nontuberculous mycobacteriosis, interstitial pneumonia, bronchitis bacterial, obstructive pulmonary disease, aplastic anaemia, pancytopenia, malignant tumour, demyelinating disorders, surgery for RA, others
History of allergy	Present, absent, unknown, undescribed
History of allergy: details	Drug, food, both, others
Smoking history	Present, absent, unknown, undescribed
Smoking history: details	Previously, currently, unknown, undescribed
RA stage/progression	Stage I, Stage II, Stage III, Stage IV, undescribed
	(It also should be tabulated by means of categories of "Stage I + II," "Stage III + IV" and "undescribed" other than the above categories)
Disability level of RA	Class I, Class II, Class III, Class IV, undescribed
	(It also should be tabulated by means of categories of "Class I + II," "Class III + IV" and "undescribed" other than the above categories)
Previous medication: DMARDs	Methotrexate (MTX), salazosulfapyridine, tacrolimus hydrate, bucillamine, others
Dose of concomitant MTX (mg/week) *1	≥ 12.0mg/week and < 14.0mg/week, ≥ 14.0mg/week and < 16.0mg/week, ≥ 16.0mg/week
Concomitant drug: DMARDs (other than MTX) *1	Present, absent
Concomitant drug: adrenocortical hormone *1	Present, absent

Data	Layer separation
Concomitant drug: DMARDs (other than MTX) *2	Present, absent
Concomitant drug: adrenocortical hormone *2	Present, absent
Concomitant drug: other concomitant drugs *2	Present, absent
DAS28-4CRP at Baseline by Category *3	<2.6, 2.6<=

*1 The concomitant drugs used at the start of Humira treatment should be included.

*2 The concomitant drugs used during the treatment with Humira should be included.

*3 The layer separation at the time of logistic regression analysis in the literature analysis should be applied.

<Treatment status>

Data	Layer separation
Mode of administration	Administration by a physician only, self-administration only, administration by a physician and self-administration
Period to treatment completion (day)*	≤ 168, ≥ 169 and ≤ 364, ≥ 365 and ≤ 728, continuing treatment *Continuing treatment should be ≥ 729 or the continued patients in the third CRF.
Dosage and administration	40 mg/biweekly, 80 mg/2 biweekly, 40 mg/biweekly or 80 mg/biweekly, other

* Patients confirmed to have longer treatment duration than 728 days and with "continuing" in the final record in the "treatment status" in the third CRF should be specified as the category of "continuing treatment."

<Reason for discontinuation>

Data	Layer separation
Reason for discontinuation (first and second CRFs)	Occurrence of AEs, inadequate response, patient refused treatment with Humira, failed to visit hospital, others [symptoms improved (including complete remission), pregnancy/desire for pregnancy, others], undescribed
Reason for discontinuation (third CRF)	Occurrence of AEs, symptom improved, inadequate response, patient refused treatment with Humira, others (pregnancy/desire for pregnancy, others), undescribed
Reason for survey discontinuation	Administration of biological products other than Humira, failed to visit hospital, others, undescribed

<Efficacy endpoints>

Data	Layer separation	
DAS28-4ESR	High	> 5.1
	Moderate	> 3.2 and ≤ 5.1
	Low	≥ 2.6 and ≤ 3.2
	Remission	< 2.6
DAS28-4CRP	High	> 5.1
	Moderate	> 3.2 and ≤ 5.1
	Low	≥ 2.6 and ≤ 3.2
	Remission	< 2.6
CDAI	High	> 22.0
	Moderate	> 10.0 and ≤ 22.0
	Low	> 2.8 and ≤ 10.0
	Remission	≤ 2.8
SDAI	High	> 26.0
	Moderate	> 11.0 and ≤ 26.0
	Low	> 3.3 and ≤ 11.0
	Remission	≤ 3.3
HAQ-DI	High	> 1.5
	Moderate	> 1.0 and ≤ 1.5
	Low	> 0.5 and ≤ 1.0
	Remission	≥ 0 and ≤ 0.5
mTSS	Change (≤ 0)	Change ≤ 0
	Change (≤ 0.5)	Change ≤ 0.5
	Change (≤ 1.0)	Change ≤ 1.0
Bone erosion score	Change (≤ 0)	Change ≤ 0
	Change (≤ 0.5)	Change ≤ 0.5
	Change (≤ 1.0)	Change ≤ 1.0
Joint space narrowing score	Change (≤ 0)	Change ≤ 0
	Change (≤ 0.5)	Change ≤ 0.5
	Change (≤ 1.0)	Change ≤ 1.0

*Hereafter, "complete remission" refers to "Remission" in the above table.

12. Handling of data on test/evaluation time

For data entered at each timing of efficacy evaluation excluding mTSS, bone erosion score and joint space narrowing score, the acceptability of data by timing should be judged based on the acceptable range of the timing. The acceptable range of the timing is shown in the table below.
If there is more than one data within the acceptable range of the timing, the data on the closest date to the reference date should be adopted. If there is more than one data within the acceptable range of the timing with the equal number of days from the reference before and after the reference date respectively, the data before the reference date should be adopted.

When evaluating efficacy regarding administration of Humira, it should follow the following provision for the data included in the following acceptable range.
・The data up to the date of final Humira treatment + 28 days should be tabulated.
However, the date of final Humira treatment +28 days is later than the date of survey discontinuation, the data up to the date of survey discontinuation should be tabulated.
This date is called [final evaluation date] in the following.

Timing and period category	Handling of data
Prior to treatment start	Data included in the period between the date of initial Humira treatment -28 days and the date of initial Humira treatment and the closest data to the date of initial Humira treatment should be adopted.
At week 12	Data included in the period between the date of initial Humira treatment +56 days and the date of initial Humira treatment +112 days and the closest data to the date of initial Humira treatment +84 days should be adopted.
At week 24	Data included in the period between the date of initial Humira treatment +140 days and the date of initial Humira treatment +196 days and the closest data to the date of initial Humira treatment +168 days should be adopted.
At week 52	Data included in the period between the date of initial Humira treatment +336 days and the date of initial Humira treatment +392 days and the closest data to the date of initial Humira treatment +364 days should be adopted.
At week 76	Data included in the period between the date of initial Humira treatment +504 days and the date of initial Humira treatment +560 days and the closest data to the date of initial Humira treatment +532 days should be adopted.
At week 104	Data included in the period between the date of initial Humira treatment +700 days and the date of initial Humira treatment +756 days and the closest data to the date of initial Humira treatment +728 days should be adopted.
At final evaluation	The final data of the patient among the data included in the period between the date of initial Humira treatment +1 day and the final evaluation date should be adopted.

For data entered at each evaluation timing of mTSS, bone erosion score and joint space narrowing score when evaluating efficacy regarding administration of Humira, the acceptability of data by timing should be judged based on the acceptable range of the timing. The acceptable range of the timing is shown in the table below.
If there is more than one data within the acceptable range of the timing, the data on the closest date to the reference date should be adopted. If there is more than one data within the acceptable range of the timing with the equal number of days from the reference before and after the reference date respectively, the data before the reference date should be adopted.
Additionally, it should follow the following provision for the data included in the following acceptable range.
・If the date up to the date of final Humira treatment +56 days, and the date of survey discontinuation is later than the date of survey discontinuation +56 days, the data up to the date of survey discontinuation should be tabulated.

Timing and period category	Handling of data
Prior to treatment start	Data included in the period between the date of initial Humira treatment -56 days and the date of initial Humira treatment +56 days and the closest data to the date of initial Humira treatment should be adopted.
At week 52	Data included in the period between the date of initial Humira treatment +308 days and the date of initial Humira treatment +420 days and the closest data to the date of initial Humira treatment +364 days should be adopted.
At week 104	Data included in the period between the date of initial Humira treatment +672 days and the date of initial Humira treatment +784 days and the closest data to the date of initial Humira treatment +728 days should be adopted.

The time for evaluation of treatment continuing group and treatment discontinued group in the third CRF should also be allocated separately. For patients whom the final Humira treatment is later than week 52 +4 weeks, the data on the latest date in the third CRF should be used as the data on the final evaluation date. However, if there is the date of survey discontinuation, the data up to the date should be used.
This date is called [final evaluation date] in the following.

At final evaluation (third CRF)	When the date of survey discontinuation is not entered: The last data of the patient among the data included in the period between the date of initial Humira treatment +504 days and the final evaluation date should be adopted. When the date of survey discontinuation is entered: The last data of the patient among the data included in the period between the date of initial Humira treatment +504 days and the final evaluation date should be adopted.

	In the treatment discontinued group, the data of which the date of treatment discontinuation and the final evaluation date are ≥ 24 weeks apart should be adopted.

Evaluation time for evaluation of treatment continuing group and treatment discontinued group in the third CRF should also be allocated separately for the data entered at the evaluation time of mTSS, bone erosion score and joint space narrowing score. For patients whom the final Humira treatment is later than week 52 +4 weeks, the data on the latest date in the third CRF should be used as the data on the final evaluation date of X-ray. However, if there is the date of survey discontinuation, the data up to the date should be used.
This date is called [final evaluation date of X-ray] in the following.

At final evaluation (third CRF)	When the date of survey discontinuation is not entered: The final data of the patient among the data included in the period between the date of initial Humira treatment +504 days and the final evaluation date of X-ray (should be later than day 505) should be adopted. When the date of survey discontinuation is entered: The final data of the patient among the data included in the period between the date of initial Humira treatment +504 days and the final evaluation date of X-ray (should be later than day 505) should be adopted. In the treatment discontinued group, the data of which the date of treatment discontinuation and the final evaluation date of X-ray are ≥ 24 weeks apart should be adopted.

When tabulating AEs by time of onset, the tabulation subjects should be decided based on the followings. If there is more than one event of the same PT in the same patient, its tabulation should be focusing on the initial occurrence.
However, when extraction conditions including seriousness and causal relationship are added to the AEs, its tabulation should be focusing on the initial occurrence after narrowing them down with the extraction conditions. In addition, the data on AEs outside the follow-up period among the data included in the following acceptable range should also be excluded from tabulation.

Timing and period category	Handling of data
Treatment start to week 24	Data included in the period between the date of initial Humira treatment and the date of initial Humira treatment +167 days should be adopted.
Week 24 to week 52	Data included in the period between the date of initial Humira treatment +168 days and the date of initial Humira treatment +363 days should be adopted.
Week 52 to week 108	Data included in the period between the date of initial Humira treatment +364 days and the date of initial Humira treatment +755 days should be adopted.
After completion of treatment	The data included in the AE follow-up period among the data on AEs occurred after completion of Humira treatment should be adopted.

13. Tables and figures to be prepared (numbers and names of Tables and Figures)

13.1. Overall

"Table 1.1 Contract with institutions and number of patients"

Analysis objects: Number of contract institutions, number of patients included in the safety analysis set, mean number of patients per institution, maximum number of patients per institution, minimum number of patients per institution

Purpose of analysis: To confirm the contract and the number of patients of the institutions.

Note: The number of contract institutions, mean number of patients per institution, maximum number of patients per institution, and minimum number of patients per institution with the patients included in the safety analysis set should be analyzed.

"Table 1.2 Patient disposition diagram"

Analysis items: Number of patients enrolled, number of patients with returned CRFs, number of patients without returned CRFs, number of patients with uncorrectable CRFs, number of patients with fixed CRFs, number of patients with unfixed CRFs, number of patients included in the safety analysis set, number of patients excluded from the safety analysis set (and by reason), number of patients included in the efficacy analysis set, number of patients excluded from the efficacy analysis set (and by reason).

Purpose of analysis: To confirm the disposition of the analysis sets.

Note: The numbers of patients should be shown in a flow chart.
The items with no reason for exclusion should not be read out for each item.

"Table 1.2 (Appendix) Patient composition diagram"

Analysis object: Number of patients included in the efficacy analysis set

Purpose of analysis: To confirm the number of patients evaluated and the number of unevaluable patients per efficacy endpoint.

Note: The numbers of patients should be shown in a flow chart.

"Table 1.2 Patient disposition diagram (third CRF)"

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

Purpose of analysis: To confirm the disposition of the number of patients per efficacy endpoint evaluable in the third CRF when allocating the patients included in the efficacy analysis set in the third CRF into the following four groups: the "treatment continuing" group, "treatment discontinued" group, "survey discontinued" group or "other" group.

Note: None in particular.

"Table 1.3.1 Progress of the CRF"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of overall patients with fixed CRFs and by CRF for the patients included in the safety analysis set and efficacy analysis set.

Note: None in particular.

"Table 1.3.2 List of patients"

Analysis object: Patients with fixed CRFs

Purpose of analysis: To confirm the details of the overall patients.

Note: To indicate the details in a list.

"Table 1.3.3 Lists of patients excluded from safety analysis set and patients excluded from efficacy analysis set (including reasons for exclusion)"

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

Purpose of analysis: To confirm the reasons for excluding from the safety analysis set and efficacy analysis set.

Note: To indicate the case numbers and reasons for exclusion in a list.
<Detailed note>
*Where one patient has more than one reason for exclusion, they should be linked with "commas" for output.

"Table 1.4 Disposition by Hospital of the University of Occupational and Environmental Health, Japan"

Analysis object: Patients included in the safety analysis set, patients included in the efficacy analysis set (DAS28-4CRP)

Purpose of analysis: To indicate the incidence of ADRs and the results of χ^2 tests in the patients included in the safety analysis set and the response rate in EULAR DAS28-4CRP and the results of χ^2 tests in EULAR DAS28-4CRP at the final evaluation in patients included in the efficacy analysis set (DAS28-4CRP) per institution analyzed (other than Hospital of the University of Occupational and Environmental Health, Japan and University of

Occupational and Environmental Health, Japan).

Note: Good Response and Moderate Response should be judged as "effective" for the EULAR DAS28-4CRP response at the final evaluation.

"Table 1.5 Disposition by mode of Humira administration"

Analysis object: Patients included in the safety analysis set, patients included in the efficacy analysis set (DAS28-4CRP)

Purpose of analysis: To indicate the incidence of ADRs and the results of χ^2 tests in the patients included in the safety analysis set and the response rate in EULAR DAS28-4CRP and the results of χ^2 tests at the final evaluation in patients included in the efficacy analysis set (DAS28-4CRP).
The category for mode of administration should follow "11. Data-layer separation."

Note: Good Response and Moderate Response should be judged as "effective" for the EULAR DAS28-4CRP response at the final evaluation.

13.2. Safety

"Table 2.1 Distribution status by patient background factor"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To calculate the number and percentage of patients by patient background factor at the start of treatment, or summary statistics by work status.
The patient background factors should follow "11. Data-layer separation."

Note: Complication: liver disorder (hepatitis) ... the denominator of the percentage should be the number of patients with "hepatitis."
Complication: liver disorder (hepatitis virus carrier) ... the denominator of the percentage should be the number of "hepatitis virus carriers."
History of allergy (details) ... the denominator of the percentage should be the number of patients "with" a history of allergy.
Smoking history (details) ... the denominator of the percentage should be the number of patients "with" a smoking history.
Smoking history: smoking years (previously) ... the denominator of the percentage should be the duration of smoking (year) of the patient "previously smoking."
Smoking history: smoking years (currently) ... the denominator of the percentage should be the duration of smoking (year) of the patient "currently smoking."
Concomitant drug ... the data at the start of Humira treatment and duration of Humira treatment should be analyzed, respectively.
<Detailed note>

1) The denominator of the percentage should be the number of patients with "hepatitis."
2) The denominator of the percentage should be the number of "hepatitis virus careers."

3) The denominator of the percentage should be the number of patients "with" a history of allergy.
4) The denominator of the percentage should be the number of patients "with" a smoking history.
5) The data on the duration of smoking (year) of the patients "previously smoking" should be analyzed.
6) The data on the duration of smoking (year) of the patients "currently smoking" should be analyzed.
7) The data at the start of Humira treatment should be analyzed.
8) The data during the Humira treatment should be analyzed.

"Table 3.1 Humira treatment status"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To calculate the number and percentage of patients or summary statistics by mode of administration and period to treatment completion concerning Humira treatment status.
The category for mode of administration should follow "11. Data-layer separation."

Note: 10.1 "Humira treatment period" should be used as the total treatment period including washout as the period to treatment completion.
<Detailed note>
1) When the patient was continuing the treatment at week 104, the patient was tabulated as "continuing treatment."

"Table 3.2.1 Disposition of reasons for discontinuation of Humira treatment (first and second CRFs)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number and percentage of patients for the disposition of the reasons for discontinuation of Humira treatment.
The reasons for discontinuation should follow "11. Data-layer separation."

Note: The denominator of the percentage of the number of discontinued patients should be the number of patients included in the safety analysis set, and the denominator of the percentage of the number of patients by reason for discontinuation should be the number of overall discontinued patients.
<Detailed note>
When a patient is applicable to more than one items, each of them was counted.

"Table 3.2.2 Disposition of reasons for survey discontinuation (third CRF)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number and percentage of patients for the disposition of the reasons for discontinuation of the survey discontinued patients in the third CRF. The number and percentage of patients should also be indicated for the

disposition of the reasons for discontinuation of the patient who discontinued treatment in the third CRF. The reasons for discontinuation should follow "11. Data-layer separation."

Note: The denominator of the percentage of the number of discontinued patients should be the number of patients with fixed CRFs at week 104 among the patients included in the safety analysis set, and the denominator of the percentage of the number of patients by reason for discontinuation should be the number of overall discontinued patients by reason for survey discontinuation and treatment discontinuation.
The patients applicable to survey discontinuation should not be included in the number of treatment discontinued patients. The reasons for treatment discontinuation should be the change in dose/number of doses or reason for discontinuation of the final record in the "Humira treatment status" in the third CRF.
<Detailed note>
When a patient is applicable to more than one items, each of them was counted.

"Table 5.1 Frequency of ADRs by seriousness"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of patients analyzed, number of patients who developed all events, number and percentage of ADRs, number and percentage of SOC and PT by seriousness regarding ADRs.
The same PT of the same patient should be summarized collectively, and in that sense, the most serious event should be tabulated.

Note: The information on novelty should not be granted.
The next forms should be prepared in the same manner.
"Table 5.1.1 Frequency of AEs by seriousness"
Analysis object: Patients included in the safety analysis set
"Table 5.1.2 Frequency of ADRs by seriousness (excluded patients)"
Analysis object: Patients excluded from the safety analysis set
Note: Among the patients with fixed CRFs, the patients excluded from the safety analysis set should be tabulated.
"Table 5.1.3 Frequency of ADRs by seriousness (Hospital of the University of Occupational and Environmental Health, Japan)"
Analysis object: Patients included in the safety analysis set
Note: patients treated at the Hospital of the University of Occupational and Environmental Health, Japan should be tabulated.
"Table 5.1.4 Frequency of ADRs by seriousness (other than Hospital of the University of Occupational and Environmental Health, Japan)"
Analysis object: Patients included in the safety analysis set
Note: Patients excluded from those treated at the Hospital of the University of Occupational and Environmental Health, Japan should be tabulated.

"Table 5.2.1 Frequency of ADRs by time of onset"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of patients analyzed, number of patients who developed all ADRs, number and percentage of ADRs, number and percentage of SOC and PT by time of onset regarding ADRs.

Note: The information on novelty should not be granted.
Categories for time of onset of ADRs: "start of treatment to week 24," "week 24 to week 52," "week 52 to week 108," and "after completion of treatment."

"Table 5.2.2 Frequency of serious ADRs by time of onset"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of patients analyzed, number of patients who developed all events, number and percentage of ADRs, number and percentage of SOC and PT by time of onset regarding serious ADRs.

Note: The information on novelty should not be granted.

"5.2.3 Summary of serious adverse drug reactions by each MTX Dose of Baseline"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of patients analyzed, number of patients who developed ADRs, number and percentage of ADRs, number and percentage of SOC and PT by category of MTX dose at the start of treatment regarding serious ADRs.

Note: Category of MTX dose at the start of treatment
"Baseline MTX 12<= <14.0," "Baseline MTX 14.0<= <16.0," "Baseline MTX 16.0<="
This should be prepared only at the time of literature analysis.

"Table 5.2.4 Summary of serious adverse drug reactions by each MTX Dose of Baseline (Event/100 Patient Years)"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of patients analyzed, number of patients who developed ADRs, number and percentage of ADRs (unit: 100 persons/year), number and percentage of SOC and PT by category of MTX dose at the start of treatment regarding serious ADRs during Humira treatment.

Note: Category of MTX dose at the start of treatment
"Baseline MTX 12<= <14.0," "Baseline MTX 14.0<= <16.0," "Baseline MTX 16.0<="
Percentage of patients who develop ADRs (person/year) = "number of serious ADRs / total follow-up period)
This should be prepared only at the time of literature analysis.

"Table 5.3.1 List of AEs occurred during treatment and after completion of treatment"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of overall ADRs, SOC and PT occurred by case status (overall, patients who are continuing Humira treatment, patients who discontinued Humira treatment) regarding AEs.
The patients who discontinued Humira treatment should be indicated by timing of treatment (during treatment, after treatment).

Note: The definitions of case status should be as follows.
・During treatment
Events that occurred between the date of initial Humira treatment and the date of final Humira treatment.
・After treatment
Events that occurred after the date of final Humira treatment.

"Table 5.3.2 List of serious AEs occurred during treatment and after completion of treatment"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the number of overall AEs, SOC and PT occurred by case status (overall, patients who are continuing Humira treatment, patients who discontinued Humira treatment) per timing of treatment (during treatment, after completion of treatment) regarding serious AEs.

Note: The definitions of the patients who are continuing Humira treatment and the patients who discontinued Humira treatment should be same as "Table 5.3.1 List of AEs occurred during treatment and after completion of treatment."

"Table 5.4 Incidence of ADRs by patient background factor"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To indicate the overall ADRs, and the number and percentage the patients who developed ADRs by seriousness by patient background factor. The categories of patient background factors should follow "11. Data-layer separation," and when ADRs of the same PT occurred in the same patient, and the number of the ADR should be rounded to a severe event before tabulation.
<Detailed note>
1) The data at the start of Humira treatment should be analyzed.
2) The data during the Humira treatment should be analyzed.
"Table 5.4.1 Incidence of ADRs by patient background factor (Hospital for the University of Occupational and Environmental Health, Japan)"
Analysis object: patients included in the safety analysis set
Note: Patients treated at the Hospital of the University of Occupational and Environmental Health, Japan should be tabulated.

"Table 5.4.2 Incidence of ADRs by patient background factor (other than Hospital for the University of Occupational and Environmental Health, Japan)"
Analysis object: patients included in the safety analysis set
Note: Patients excluded from those treated at the Hospital of the University of Occupational and Environmental Health, Japan should be tabulated.

"Table 5.5.1.1 Frequency of ADRs by seriousness with or without liver disorder"
Analysis object: Patients included in the safety analysis set
Purpose of analysis: To indicate the number of patients analyzed, number of patients who developed ADRs, number and percentage of ADRs, number and percentage of SOC and PT by seriousness with or without liver disorder regarding ADRs. Additionally, the stratified items with a significant difference in Table 5.4 should also be tabulated.
Note: The information on novelty should not be granted. This should be prepared only when there are more than ten patients or 3% of the patients are applicable to the category of interest.
The next forms should be prepared in the same manner.
"Table 5.5.1.2 Frequency of ADRs by seriousness with or without renal disorder"
Note: The categories of the tabulation should be with or without renal disorder.
"Table 5.5.1.3 Frequency of ADRs by seriousness in elderly or non-elderly"
Note: The categories of the tabulation should be by elderly or non-elderly.
"Table 5.5.1.4 Frequency of ADRs by seriousness by mode of Humira administration"
Note: The categories of the tabulation should follow the mode of Humira administration in Table 3.1.

"Table 5.5.2.1 Frequency of ADRs by outcome with or without liver disorder"
Analysis object: Patients included in the safety analysis set
Purpose of analysis: to indicate the number of patients analyzed, number of patients who developed all ADRs, number and percentage of ADRs, number and percentage of SOC and PT with or without liver disorder by outcome regarding ADRs.
Note: The information on novelty should not be granted.
This should be prepared only when there are more than ten patients or 3% of the patients are applicable to the category of interest.
The next forms should be prepared in the same manner.
"Table 5.5.2.2 Frequency of ADRs by outcome with or without renal disorder"
Note: The categories of the tabulation should be with or without renal disorder.

"Table 5.5.2.3 Frequency of ADRs by outcome by elderly or non-elderly"
Note: The categories of the tabulation should be by elderly or non-elderly.
"Table 5.5.2.4 Frequency of ADRs by outcome by mode of Humira administration"
Note: The categories of the tabulation should follow the mode of Humira administration in Table 3.1.

"Table 5.6 Appended Form 2"
Analysis object: Patients included in the safety analysis set
Purpose of analysis: To prepare for reexamination.
Note: None in particular.

"Table 5.7 Appended Form 3"
Analysis object: Patients with fixed CRFs
Purpose of analysis: To indicate a list of summaries of the patients surveyed.
Note: A specification should be prepared separately for the details of analysis specification.

"Table 5.8.1 The Number of Weeks to Discontinuation"
Analysis object: Patients included in the safety analysis set
Purpose of analysis: To illustrate the survival curve of the rate of Humira continuation up to week 104. The survival curve should be illustrated by means of the SAS LIFETEST procedure.
Note: This form should be prepared only at the time of literature analysis.

"Table 5.8.2 The Number of Weeks to Discontinuation"
Analysis object: Patients included in the safety analysis set
Purpose of analysis: To illustrate the survival curve of the rate of Humira continuation up to week 104. The survival curve should be illustrated by using the SAS LIFETEST procedure, and the patients who are continuously receiving Humira even after Day 728 should be handled as the censored cases.
Note: This form should be prepared only at the time of literature analysis.

13.3. Efficacy

"Table 6.1 DAS28-4ESR response, trend, percentage of remission"
Analysis object: Patients included in the efficacy analysis set (DAS28-4ESR)
Purpose of analysis: To indicate the number of patients and summary statistics of the score and response by evaluation time for the DAS28-4ESR and conduct a paired t test for the response from baseline. In addition, the number and the percentage of patients, number of patients with Low+Remission and Remission, point estimate and 95% CI of the percentage by DAS28-4ESR category by evaluation time should be indicated, and McNemer test should be performed

for the percentage change from baseline. The DAS28-4ESR category should follow “11. Data-layer separation.”

Note: The same form should also be prepared in literature analysis.

“Table 6.1.2 Response and trend in efficacy endpoints, and percentage of complete remission (third CRF)”

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

Purpose of analysis: To tabulate the efficacy evaluation in the third CRF by efficacy endpoint. In this occasion, the patients evaluated by endpoint should be categorized by the continuing group and the discontinued group, the number of patients by evaluation time and the summary statistics of the score and the response should be indicated, and a paired t test for the response from baseline should be conducted. Additionally, the number of the patients for each efficacy endpoint category by evaluation time should be shown. The category of each efficacy endpoint should follow “11. Data-layer separation.”

Note: Continuing group...

Corresponding to the definition of the treatment continued group in “10. Derivation and calculation methods”

Discontinued group...

Corresponding to the definition of the treatment discontinued group in “10. Derivation and calculation methods”

Last observation...

Corresponding to the definition of the final evaluation time in “12. Handling of data on test/evaluation time (third CRF).”

“Table 6.1.3 Change of DAS28-4ESR Over Time (literature analysis)”

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

Purpose of analysis: To illustrate the number of patients by DAS28-4ESR category by evaluation time in histogram.

Note: Last observation ... Corresponding to the definition at the final evaluation in “12. Handling of data on test/evaluation time.”

The next forms should be tabulated in the same manner.

“Table 6.2.3 Change of DAS28-4CRP Over Time”

Note: The patients included in the efficacy analysis set (DAS28-4CRP) should be handled as the analysis objects and tabulated by DAS28-4CRP category.

“Table 6.3.1 Change of CDAI Over Time”

Note: The patients included in the efficacy analysis set (CDAI) should be handled as the analysis objects and tabulated by CDAI category.

“Table 6.4.1 Change of SDAI Over Time”

Note: The patients included in the efficacy analysis set (SDAI) should be handled as the analysis objects and tabulated by SDAI category.

"Table 6.5.1 Change of HAQ-DI Over Time"
Note: The patients included in the efficacy analysis set (HAQ-DI) should be handled as the analysis objects and tabulated by HAQ-DI category.

The above figures and tables should be prepared only at the time of literature analysis.

"Table 6.2 DAS28-4CRP response, trend, percentage of remission"
Analysis object: Patients included in the efficacy analysis set (DAS28-4CRP)
Purpose of analysis: To indicate the number of patients and summary statistics of the score and response by evaluation time for the DAS28-4CRP and conduct a paired t test for the response from baseline. In addition, the number and the percentage of patients, number of patients with Low+Remission and Remission, point estimate and 95% CI of the percentage by DAS28-4ESR category by evaluation time should be indicated, and McNemer test should be performed for the percentage change from baseline.
The DAS28-4CRP category should follow "11. Data-layer separation."
Note: The same form should also be prepared in literature analysis.

"Table 6.2.2 Summary of DAS28-4CRP by each Visit per Increase/decrease MTX Dose of up to Week 52 (literature analysis)"
Analysis object: Patients included in the efficacy analysis set (DAS28-4CRP)
Purpose of analysis: To indicate the number of patients by evaluation time, and the summary statistics of the scores and response for the DAS28-4CRP scores stratified by the groups based on the increase and decrease of MTX dose at week 52 and conduct a paired t test for the response from baseline.
The response should be compared between the groups by analysis of variance by evaluation time.
Note: It should be categorized by the following three categories based on the increase and decrease of the MTX dose from the start of Humira treatment to week 52: "2 <=," "-2 < < 2," and "< -2."
This form should be prepared only at the time of literature analysis.

"Table 6.2.4 Summary of DAS28-4CRP by each Visit per Baseline MTX Dose"
Analysis object: Patients included in the efficacy analysis set (DAS28-4CRP)
Purpose of analysis: To indicate the number of patients by evaluation time, and summary statistics of the score and response for the DAS28-4CRP score by the group of MTX dose at the start of Humira treatment.
In addition, paired t tests should be performed for the response from the start of treatment, and the results of intergroup comparison by analysis of variance should be calculated by evaluation time.
Note: The group separation should follow the concomitant MTX dose (mg/week) in the patient background in "11. Data-layer separation."

This form should be prepared only at the time of literature analysis.

"Table 6.2.5 Summary of DAS28-4CRP by each Visit per Average Usage MTX Dose of up to week 52"

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

Purpose of analysis: To indicate the number of patients by evaluation time, and summary statistics of the score and response for the DAS28-4CRP score by two groups of the mean MTX dose at week 52: < 12.0 mg/week group or ≥ 12.0 mg/week group. In addition, paired t tests should be performed for the response from baseline, and the results of intergroup comparison by analysis of variance should be calculated by evaluation time.

Note: It should be categorized by the following two categories based on the increase and decrease of the mean MTX dose from the start of Humira treatment to week 52: "< 12.0" and "12.0 <=."
This form should be prepared only at the time of literature analysis.

"Table 6.2.6 Univariate logistic analysis event: DAS28-4CRP ≤2.6 at week 104"

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

Purpose of analysis: To conduct univariate logistic regression analysis with the number of patients meeting the week 104 DAS28-4CRP < 2.6 as the objective variable and each patient background factor as the explanatory variable, and to indicate the number of patients analyzed, number of patients who developed ADRs, incidence rate, odds ratio, CI and p values.
To handle the followings as the categorical data: [consultation category (outpatient, inpatient)], [gender (male, female)], [age category (< 15, ≥ 15 and < 30, ≥ 30 and < 50, ≥ 50 and < 65, and ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85)], [age category: (< 15, ≥ 15 and < 65, ≥ 65)], [weight category (< 30, ≥ 30 and < 40, ≥ 40 and < 50, ≥ 50 and < 60, ≥ 60)], [category for duration of illness (< 3 months, ≥ 3 months and < 6 months, ≥ 6 months)], [complication (present, absent)], [smoking history (absent, present)], [RA stage/progression (Stage I/Stage II, Stage III/Stage IV)], [RA disability level (Class I/Class II, Class III/Class IV)], [past history (absent, present)], [history of allergy (absent, present)], [MTX at treatment start (≥ 12.0mg/week and < 14.0mg/week, ≥ 14.0mg/week and < 16.0mg/week, ≥ 16.0mg/week)], [DMARDs at treatment start (excluding MTX) (absent, present)], [adrenocortical hormones at treatment start (absent, present)], [DMARDs during treatment (absent, present)], [adrenocortical hormones during treatment (absent, present)], [other concomitant drugs during treatment (absent, present)], [DAS28-4CRP at treatment start (< 2.6, 2.6<=)]; and also indicate the results for [age], [weight], [duration of illness] and [DAS28-4CRP at treatment start] as the quantitative data.

Note: This form should be prepared only at the time of literature analysis.

"Table 6.2.7.1 DAS28-4CRP Score of Week 24 and Mean Usage MTX dose Change from Week 24 to Week 52"

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

Purpose of analysis: Regarding the frequency of DAS28-4CRP Remission (< 2.6) at week 24, indicate from week 24 to week 52 by MTX dose reduction and compare them between the factors by χ^2 test.
Furthermore, a scatter graph with the DAS28-4CRP score at week 12 by patient as the Y axis and the change in MTX dose from week 24 to week 52 as the X axis should also be illustrated.

Note: The following tables should also be created with the same layout .
"Table 6.2.7.2 DAS28-4CRP Score of Week 24 and Mean Usage MTX dose Change from Week 24 to Week 104"
Note: The change in MTX dose from week 24 to week 104 should be compared in this form.
"Table 6.2.7.3 DAS28-4CRP Score of Week 12 and Mean Usage MTX dose Change from Week 12 to Week 52"
Note: The change in MTX dose from week 12 to week 52 and DAS28-4CRP Remission (< 2.6) at week 12 should be compared in this form.
"Table 6.2.7.4 DAS28-4CRP Score of Week 12 and Mean Usage MTX dose Change from Week 12 to Week 104"
Note: The change in MTX dose from week 12 to week 104 and DAS28-4CRP Remission (< 2.6) at week 12 should be compared in this form.

"Table 6.3 CDAI response, trend, percentage of remission"

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

Purpose of analysis: To indicate the number of patients by evaluation time and summary statistics of the score and response for CDAI and conduct a paired t test for the response from baseline.
In addition, the number and the percentage of patients, number of patients with Low+Remission and Remission, point estimate of the percentage and 95% CI by CDAI category by evaluation time should be indicated, and McNemer test should be performed for the percentage change from baseline.
The CDAI category should follow "11. Data-layer separation."

Note: The same tabulation should also be conducted for literature analysis.

"Table 6.4 SDAI response, trend, percentage of remission"

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

Purpose of analysis: To indicate the number of patients by evaluation time and summary statistics of the score and the response for SDAI and conduct a paired t test for the response from baseline.
In addition, the number and the percentage of patients, number of patients with Low+Remission and Remission, point estimate of the percentage and

95% CI by SDAI category by evaluation time should be indicated, and McNemer test should be performed for the percentage change from baseline.
The SDAI category should follow “11. Data-layer separation.”

Note: The same form should also be prepared in literature analysis.

“Table 6.5 Trends in HAQ”

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

Purpose of analysis: To indicate the number of patients by evaluation time and summary statistics of the score and the response for HAQ and conduct a paired t test for the response from baseline.
In addition, the number and the percentage of patients, number of patients with Remission, point estimate of the percentage and 95% CI by HAQ category by evaluation time should be indicated, and McNemer test should be performed for the percentage change from baseline.
The HAQ category should follow “11. Data-layer separation.”

Note: The same form should also be prepared in literature analysis.

“Table 6.6 Trends in EQ-5D”

Analysis object: Patients included in the efficacy analysis set (EQ-5D)

Purpose of analysis: To indicate the number of patients by evaluation time, and the summary statistics of the score and the response for EQ-5D.
Moreover, a paired t test should be performed for the response from baseline.

Note: The same form should also be prepared in literature analysis.

“Table 6.7 Response and trends in other efficacy endpoints”

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

Purpose of analysis: To indicate the number of patients by evaluation time, and the summary statistics of the score and the response for other efficacy endpoints shown below.
Moreover, a paired t test should be performed for the response from baseline.
<Other endpoints>
Tender joint count, swollen joint count, global assessments of disease activity by the patient (VAS), global assessments of disease activity by a physician (VAS), ESR, CRP

Note: None in particular.

“Table 6.8.1 Response rate by patient background factor (EULAR response: DAS28-4CRP)”

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

Purpose of analysis: To indicate the number and percentage of eligible patients by patient background factor.
The patient background factors should follow “Table 5.4 Incidence of ADRs by patient background factor.”

Note: Good Response and Moderate Response should be judged as “effective” for

the EULAR DAS28-4CRP response at the final evaluation.

The next forms should be tabulated in the same manner.
"Table 6.8.1.1 Response rate by patient background factor (EULAR response: DAS28-4CRP) (Hospital of the University of Occupational and Environmental Health, Japan)"
Analysis object: Patients included in the efficacy analysis set
Note: Patients treated at the Hospital of the University of Occupational and Environmental Health, Japan should be tabulated.
"Table 6.8.1.2 Response rate by patient background factor (EULAR response: DAS28-4CRP) (other than Hospital of the University of Occupational and Environmental Health, Japan)"
Analysis object: Patients included in the efficacy analysis set
Note: Patients excluded from those treated at the Hospital of the University of Occupational and Environmental Health, Japan should be tabulated.

"Table 6.8.2. Distribution status of EULAR judgement criteria for response (DAS28-4CRP)"
Analysis object: Patients included in the efficacy analysis set (DAS28-4CRP)
Purpose of analysis: To indicate the number and percentage of patients by EULAR judgement criteria for response by evaluation time, the number and percentage of eligible patients, and 95% CI of the response rate in DAS28-4CRP.
Note: Good Response and Moderate Response should be judged as "effective" for the EULAR DAS28-4CRP response.

The next form should be tabulated in the same manner.
"Table 6.8.3 EULAR judgment criteria for response (DAS28-4ESR)"
Note: The patients analyzed should be tabulated as the patients included in the efficacy analysis set (DAS28-4ESR).

"Table 6.8.4.X Distribution status of EULAR judgment criteria for response by patient background factor (DAS28-4CRP)"
Analysis object: Patients included in the efficacy analysis set (DAS28-4CRP)
Purpose of analysis: To indicate the distribution status of EULAR judgement criteria for response by patient background factor.
Note: The same tabulation of "Table 6.8.1 Distribution status of EULAR judgement criteria for response (DAS28-4CRP)" by category of patient background factor with a significant difference with p value in χ^2 test in "Table 6.8.1." should be conducted.

"Table 6.9.1.1 Percentage of patients without a trend or worsening of mTSS (at week-52 evaluation time)"
Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)

Purpose of analysis: To indicate the number of patients by evaluation time and the summary statistics of the score and the response for mTSS and conduct a paired t test for the response from baseline. Additionally, the number and percentage of the patients by evaluation time by mTSS category should be shown. The mTSS category should follow "11. Data-layer separation."

Note: None in particular.

"Table 6.9.1.2 Percentage of patients without a trend or worsening of mTSS (at week-104 evaluation time)"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 104)

Purpose of analysis: To indicate the number of patients by evaluation time and the summary statistics of the score and the response for mTSS and conduct a paired t test for the response from baseline. Additionally, the number and percentage of the patients by evaluation time by mTSS category should be shown. The mTSS category should follow "11. Data-layer separation."

Note: None in particular.

"Table 6.9.2 Response and trends in mTSS, and percentage of complete remission (third CRF)"

Analysis object: Patients included in the efficacy analysis set (mTSS in the third CRF)

Purpose of analysis: To categorize the patients by the continuing group and the discontinued group, indicate the number of patients by evaluation time and the summary statistics of the score and the response for mTSS, and conduct a paired t test for the response from baseline. Additionally, the number and percentage of the patients by evaluation time by mTSS category should be shown. The mTSS category should follow "11. Data-layer separation."

Note: Continuing group...

Corresponding to the definition of the treatment continued group in "10. Derivation and calculation methods"

Discontinued group...

Corresponding to the definition of the treatment discontinued group in "10. Derivation and calculation methods"

Last observation...

Corresponding to the definition of the final evaluation time in "12. Handling of data on test/evaluation time (third CRF)."

"Table 6.9.3.1 mTSS Remission Rate at Week 52"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)

Purpose of analysis: To indicate the number and percentage of patients who achieved the mTSS change ($\leq 0.5, \leq 0, \leq 1$) at week 52, respectively. In addition, the distribution of mTSS changes at week 52 as the Y axis and mTSS change at week 52 of which the percentage of the patients analyzed with the mTSS change in the ascending order as the X axis should also be illustrated.

Note: This form should be prepared only at the time of literature analysis.

"Table 6.9.3.2 mTSS Remission Rate at Week 104"

Analysis object: patients included in the efficacy analysis set (mTSS at week 104)

Purpose of analysis: To indicate the number and percentage of patients who achieved the mTSS changes (≤ 0.5, ≤ 0, ≤ 1) at week 104, respectively. In addition, the distribution of mTSS change at week 104 as the Y axis and mTSS changes at week 104 of which the percentage of the patients analyzed with the mTSS change in the ascending order as the X axis should also be illustrated.

Note: This form should be prepared only at the time of literature analysis.

"Table 6.9.4.1 Correlation of Subjective background (Spearman's rank correlation coefficient) at the mTSS Remission by Week 52"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)

Purpose of analysis: To indicate the correlation with the patient background items for the patients who achieved mTSS change below 0.5 at week 52. Patient background items and categories are shown below.

<Patient background item>	<Included data>
Consultation category	Outpatient, inpatient
Gender	Male, female
Age	Continuous value
Age category 1	Aged < 15, 15<= <30, 30<= <50, 50<= <65, 65 <= < 75, 75<= < 85, <= 85
Age category 2	Aged < 15, 15 <= <65, <=65
Weight	Continuous value
Weight category	< 30, 30<= <40, 40<= <50, 50<= <60, <=60
Duration of illness	Continuous value
Category of duration of illness	< 3, 3<= <6, <=6
Complication	Present, absent
Smoking history	Present, absent
RA stage/progression	Stage I, Stage II, Stage III, Stage IV
Disability level of RA	Class I, Class II, Class III, Class IV
Past history	Present, absent
History of allergy	Present, absent
MTX at treatment start	<=12.0 <14.0,<=14.0 <16.0,<=16.0
DMARDs at treatment start (excluding MTX)	Present, absent
Adrenocortical hormones at treatment start	Present, absent
DMARDs during treatment	Present, absent
Adrenocortical hormones during treatment	Present, absent
Other concomitant drugs during treatment	Present, absent

DAS-28CRP at treatment start	Continuous value
Category of DAS-28CRP at treatment start	<2.6,2.6<=

Note: To indicate Spearman rank correlation coefficient and its p value should be indicated for correlation coefficient.
This form should be prepared only at the time of literature analysis.

"Table 6.9.4.2 Correlation of Subjective background (Spearman's rank correlation coefficient) at the mTSS Remission by Week 104"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 104)

Purpose of analysis: To indicate the correlation with the patient background items for the patients who achieved mTSS change below 0.5 at week 104 by using the same technique as Table 6.9.4.1.

"Table 6.9.5.1 Univariate logistic analysis event: <=0.5 delta mTSS at 52 week"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)

Purpose of analysis: To conduct univariate logistic regression analysis with the number of patients meeting the week-52 mTSS change ≤ 0.5 as the objective variable and each patient background factor as the explanatory variable, and to indicate the number of patients analyzed, number of patients who developed ADRs, incidence rate, odds ratio, CI and p values.
To handle the followings as the category data: [consultation category (outpatient, inpatient)], [gender (male, female)], [age category (< 15, ≥ 15 and < 30, ≥ 30 and < 50, ≥ 50 and < 65, and ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85)], [age category: (< 15, ≥ 15 and < 65, ≥ 65)], [weight category (< 30, ≥ 30 and < 40, ≥ 40 and < 50, ≥ 50 and < 60, ≥ 60)], [category for duration of illness (< 3 months, ≥ 3 months and < 6 months, ≥ 6 months)], [complication (present, absent)], [smoking history (absent, present)], [RA stage/progression (Stage I/Stage II, Stage III/Stage IV)], [RA disability level (Class I/Class II, Class III/Class IV)], [past history (absent, present)], [history of allergy (absent, present)], [MTX at treatment start (≥ 12.0mg/week and < 14.0mg/week, ≥ 14.0mg/week and < 16.0mg/week, ≥ 16.0mg/week)], [DMARDs at treatment start (excluding MTX) (absent, present)], [adrenocortical hormones at treatment start (absent, present)], [DMARDs during treatment (absent, present)], [adrenocortical hormones during treatment (absent, present)], [other concomitant drugs during treatment (absent, present)], [DAS28-4CRP at treatment start (< 2.6, 2.6<=)]; and also indicate the results for [age], [weight], [duration of illness] and [DAS28-4CRP at treatment start] as the quantitative data.

Note: This form should be prepared only at the time of literature analysis.

"Table 6.9.5.2 Univariate logistic analysis event: <=0.5 delta mTSS at 104 week"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 104)

Purpose of analysis: To tabulate the number of patients satisfying week 104 mTSS change below 0.5 as the objective variance by using the same technique as Table 6.9.5.1.

"Table 6.9.6.1 Multivariate logistic analysis event: <= 0.5 delta mTSS at 52 week"
Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)
Purpose of analysis: To conduct multivariate logistic regression analysis with the number of patients meeting the week 52 mTSS change ≤ 0.5 as the objective variable and each patient background factor as the explanatory variable, and to indicate the number of patients analyzed, number of patients who developed ADRs, incidence rate, odds ratio, CI and p values. [Gender (male, female)], [complication (absence, presence)] and [progression (Stage I/Stage II, Stage III/Stage IV)] should be handled as categorical data for the patient background factors, and the results should be indicated as the quantitative data for [duration of illness].
Note: This form should be prepared only at the time of literature analysis.

"Table 6.9.6.2 Multivariate logistic analysis event: <= 0.5 delta mTSS at 104 week"
Analysis object: Patients included in the efficacy analysis set (mTSS at week 104)
Purpose of analysis: To tabulate the number of patients satisfying week 104 mTSS change below 0.5 as the objective variance by using the same technique as Table 6.9.6.2.

"Table 6.10.1 Percentage of patients without a trend or worsening of the bone erosion score (evaluation time at week 52)"
Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)
Purpose of analysis: To indicate the number of patients and summary statistics of the score and response by evaluation time for the bone erosion score and conduct a paired t test for the response from baseline.
Additionally, the number and percentage of the patients by evaluation time by the category of the bone erosion score should be shown.
The category of the bone erosion score should follow "11. Data-layer separation."
Note: None in particular.

"Table 6.10.2 Percentage of patients without a trend or worsening of bone erosion score (evaluation time at week 104)"
Analysis object: Patients included in the efficacy analysis set (mTSS at week 104)
Purpose of analysis: To tabulate the patients included in the efficacy analysis set (mTSS at week 104) by using the same tabulation technique as Table 6.10.1.
Note: None in particular.

"Table 6.11.1 Percentage of patients without a trend or worsening of the joint space narrowing score (evaluation time at week 52)"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 52)

Purpose of analysis: To indicate the number of patients by evaluation time and the summary statistics of the score and the response for the joint space narrowing score and conduct a paired t test for the response from baseline.
Additionally, the number and percentage of the patients by evaluation time by the category of the joint space narrowing score should be shown.
The category of the joint space narrowing score should follow "11. Data-layer separation."

Note: None in particular.

"Table 6.11.2 Percentage of patients without a trend or worsening of the joint space narrowing score (evaluation time at week 104)"

Analysis object: Patients included in the efficacy analysis set (mTSS at week 104)

Purpose of analysis: To tabulate the patients included in the efficacy analysis set (mTSS at week 104) by using the same tabulation technique as Table 6.11.1.

Note: None in particular.

"Table 7.1 Summary of MTX at each Period"

Analysis object: patients included in the safety analysis set

Purpose of analysis: to calculate the summary statistics of the MTX dose at treatment start, the mean MTX dose between treatment start and week 52, the mean MTX dose between treatment start and week 12, and the mean MTX dose between week 12 and week 52.

Note: This form should be prepared only at the time of literature analysis.

"Table 7.1.1 Summary of MTX Over Time"

Analysis object: Patients included in the safety analysis set

Purpose of analysis: To illustrate the followings by timing by a cumulative bar chart: MTX dose at treatment start, MTX dose at week 12, MTX dose at week 24, MTX dose at week 52, MTX dose at week 76, and MTX dose at week 104.
At treatment start, at weeks 12, 24, 52, 76 and 104 should be established by the categories indicated in "12. Handling of data on test/evaluation time."

Note: This form should be prepared only at the time of literature analysis.

"Table 7.1.2 Demographic data and baseline score each MTX Dose of Baseline"

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: To calculate the number and percentage of patients by patient background factor at the start of treatment, or the stratified summary statistics of MTX dose at the start of Humira treatment.
The patient background factors should follow "11. Data-layer separation."

Note:

[Complication: liver disorders (hepatitis)]: The denominator of the percentage should be the number of patients with “hepatitis.”
[Complication: liver disorders (hepatitis virus carrier)]: The denominator of the percentage should be the number of “hepatitis virus carriers.”
[History of allergy: details]: The denominator of the percentage should be the number of patients “with” a history of allergy.
[Smoking history: details]: The denominator of the percentage should be the number of patients “with” a smoking history.
[Smoking history: smoking years (previously)]: The denominator of the percentage should be the duration of smoking (year) of the patient “previously smoking.”
[Smoking history: smoking years (currently)]: The denominator of the percentage should be the duration of smoking (year) of the patient “currently smoking.”
[Concomitant drug]: The data at the start of Humira treatment and duration of Humira treatment should be analyzed, respectively.
This form should be prepared only at the time of literature analysis.

“Table 7.1.3 Demographic data and baseline score each MTX Dose of Baseline”

Analysis object: Patients included in the efficacy analysis set

Purpose of analysis: To calculate the number and percentage of patients by patient background factor at the start of treatment, or the summary statistics by the stratified MTX dose at the start of Humira treatment. The frequency and the percentage of each stratification of the categorical data should be calculated for patient background factors, and the summary statistics should be calculated for quantitative data.

Note: This form should be prepared only at the time of literature analysis.

“8.1 List of Demographic data and Efficacy data”

Analysis object: Patients with fixed CRFs

Purpose of analysis: Among the efficacy endpoints, DAS28-4CRP, DAS28-4ESR, CDAI, SDAI, HAQ-DI, and EQ-5D scores at the start of Humira treatment, the scores and the change at week 52, the scores and the change at week 104, and at the final evaluation should be read out with patient background information.
Additionally, of the efficacy endpoints, mTSS score at each reading session of X-ray score should be indicated. The scores at the start of Humira treatment and week 52, and the change at week 52 at the first reading session should be shown as a list with the flag information that can identify the mTSS change at week 52 as additional information: ≤ 0 (No Progression), ≤ 0.5 (Structural Remission), ≥ 3.0, and > 10.0 (Rapid Progression).
When using the scores of the second reading session, the scores and the change at week 104 should be indicated in a list, and the flag information that can identify the change at 104 should be indicated as additional

information: ≤ 0 (No Progression), ≤ 0.5 (Structural Remission), ≥ 3.0, and > 10.0 (Rapid Progression).

Note: This form should be prepared only at the time of literature analysis.

"8.2 List of Discontinuation of ADA Group by Questionnaire Part III"

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

Purpose of analysis: To indicate the efficacy evaluation for the patients evaluated for efficacy in the third CRF as a list.

Note: None in particular.

14. Tabulation history

14.1. List of tabulation histories

Described in the plan for analysis diagram outputs.

14.2. Reason for cancellation of creation of diagrams

None in particular.