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EMEA/H/C/54001/2015
Human Medicines Development and Evaluation

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Enbrel

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/000262/P46 163

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Introduction

On 20 October 2014, the MAH submitted a completed paediatric study for Enbrel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that “A long-term, open-label study of TNR-001 in Japanese Juvenile Idiopathic Arthritis Subjects, study number 0881A1-207-JA” is a stand-alone study

1.2. Information on the pharmaceutical formulation used in the study

Etanercept was supplied in vials as a sterile lyophilized powder containing 25 mg of etanercept, mannitol, sucrose, and tromethamol. The diluent for rehydration of etanercept was sterile water for injection provided in prefilled syringes. Once reconstituted, etanercept was stable for injection for up to 6 hours if kept refrigerated at 2°C to 8°C.

The test article was administered only to subjects who were eligible and had provided signed informed consent. Each subject was treated 0.2 or 0.4 mg/kg TNR-001 SC injection twice weekly by self-injection or by his/her guardian.

1.3. Clinical aspects

1.3.1. Introduction

Etanercept belongs to the pharmacological class of tumour necrosis factor-alpha (TNF-α) inhibitors (Anatomical Therapeutic Chemical [ATC] code: L04AB01). Etanercept is a bioengineered fusion protein incorporating 2 molecules of soluble tumour necrosis factor (TNF) receptor p75 and the crystallisable fragment (Fc) component of immunoglobulin G1 (IgG1). This human recombinant product binds specifically to TNF-α and lymphotoxin, inhibiting their interaction with cell surface receptors. Etanercept is effective in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and psoriasis, and has a well-defined and acceptable risk-benefit ratio.

The MAH has submitted a study report for a Japanese study in JIA subjects (0881A1-207-JA; Study Dates: 25 August 2005 through 03 September 2009) for the product etanercept.

Although the main body of the report has been translated into the English language , the protocol and other appendices are presented in Japanese. This exercise has , at times, hampered interpretation of the data.

Even though the protocol/CSR refers to JRA, subjects are referred to as JIA in the clinical overview based on the current terminology.

Currently International League of Associations for Rheumatology use the terminology of international standards, juvenile idiopathic arthritis, JIA as a compromise in terms of the JRA in US and JCA in EU, however in this report, JRA was used because “JRA core set” as the standard efficacy criteria in US was used in this study.

1.3.2. Clinical study

A long-term, open-label study of TNR-001 in Japanese Juvenile Idiopathic Arthritis Subjects. **No.:**

0881A1-207-JA

Description

Methods

Objective(s)

The primary objective of the study was to assess the safety of the long-term administration of TNR-001 in patients with active polyarticular course JIA.

The secondary objective of the study was to assess the efficacy of the long-term administration of etanercept in subjects with active polyarticular-course JIA.

Study design

This clinical study was an open-label study to evaluate the safety and efficacy of TNR-001 administered subcutaneously at a dose of 0.2 or 0.4 mg/kg (up to a maximum of 12.5 or 25 mg) twice weekly in patients with polyarthritis type of active juvenile idiopathic arthritis (JIA) who previously participated in the JIA studies, 0881A1-204, 0881A1-206-JA or 0881A1-208-JA.

The dose levels for individual subjects were same as the dose in the previous studies since the subjects with no safety concern were enrolled in this study. For subjects in 0.2 mg/kg dose group who met the criteria of dose up because of remission 0.4 mg/kg dose were administered after week 4 evaluation. For subjects in 0.4 mg/kg dose group who met the critedia of dose down because of safety concern 0.2 mg/kg were administered after week 4 evaluation.

Study population /Sample size

A total of 32 subjects with polyarticular JIA, who had been enrolled in the previous studies (Studies 204-JA, 206-JA or 208-JA), were considered to be appropriate for enrolment into study 0881A1-207-JA by the investigator or sub-investigators.

Inclusion Criteria

Subjects who satisfied the following inclusion criteria were eligible to participate in this study if all other qualifying criteria were met:

1. Patients who completed the 204, 206-JA or 208-JA studies didn't have any safety concern in the previous studies, and the investigator judged it was proper them to be move to this study.
2. The subjects have consented to practice proper contraception during the study, if male children of reproductive capacity or female children of child-bearing potential.
3. The subjects have given informed assent to participate in the study, and whose legal guardian has given informed consent. For children under 7 years of age, the acquisition of informed assent may not necessarily be required.
4. The subjects should have legal guardians who can properly manage the storage and administration of the test article and can accurately record the time of administration, and the physical condition of the subject, etc. in the patient diary.

Exclusion Criteria

Subjects were ineligible to participate in this study if any of the following criteria were met:

1. Patients who failed to meet the restrictive conditions regarding concomitant medications or treatment.
2. Any others judged ineligible for participation in the study by the investigator or the sub-investigator.
3. Patients with a present or past psychiatric disorder that may obstruct compliance with the protocol or acquisition of informed consent or assent and patients whose legal guardian

Treatments

Etanercept was supplied in vials as a sterile lyophilized powder containing 25 mg of etanercept, mannitol, sucrose, and tromethamol. The diluent for rehydration of etanercept was sterile water for injection provided in prefilled syringes. Once reconstituted, etanercept was stable for injection for up to 6 hours if kept refrigerated at 2°C to 8°C.
The test article was administered only to subjects who were eligible and had provided signed informed consent. Each subject was treated 0.2 or 0.4 mg/kg TNR-001 SC injection twice weekly by self-injection or by his/her guardian.

Selection of Treatment Regimen

In the phase 2 clinical study (0881A1-204) conducted in Japan, in which the drug was administered subcutaneously at a dose of 4 mg/kg twice weely as the approved dosage overseas, TNR-001 was well tolerate and showed high efficacy response. Comparing these results with the results of the phase 2 clinical study (16.0016) conducted in the US, JRA30%DOI and the serum concentration of TNR-001 were highter in Japanese subjects and more adverse events were reported in study 204. Therefore, 2 phase 2 studies (0881A1-206-JA and 0881A1-208-JA) were conducted with the lower dose, 0.2 mg/kg twice weely. In addition, the subjects treated in these 3 Japanese studies and had no safety concern could join the long-term study, 0881A1-207-JA. The subjects were initially treated with the dose that the subjects received in the previous

studies.

Change of Dosage during the Study

The investigators could change the dosage reduced to 0.2 mg/kg for the subjects who were treated 0.4 mg/kg because of the safety reason.

The investigators could change the dosage increased to 0.4 mg/kg for the subjects who were treated 0.2 mg/kg, considering the clinical response and efficacy, such change of the JRA core sets according to the criteria shown in Table 6-1.

Table 6-1: Criteria for the Increasing Dosage

	In the case for the subjects correspond to all three criteria, the dosage was increased
1.	3 and more categolies of 6 JRA core sets were worsen ≥15% compared with the value at the baseline of this study.
2.	1 or less categolies of 6 JRA core sets were improved ≥15% compared with the value at the baseline of this study.
3.	The subject have ≥2 active joints.

Outcomes/endpoints

Primary Outcome/Efficacy Variables

The primary efficacy endpoint was the JIA core set consisting of physician's global assessment, subject or guardians global assessment, number of active joints, number of painful joints on pressure or motion, quality of life as assessed by Childhood Health Assessment Questionnaire (CHAQ) and erythrocyte sedimentation rate (ESR) and other disease activity variables.

Secondary Outcome/Efficacy Variables:

The secondary efficacy endpoints were JIA 30% Definition of Improvement (DOI), JIA 50% DOI, JIA 70% DOI, percent change of the JIA core set and other disease activity variables (except for rheumatoid factor), serum cytokine concentration (Interleukin [IL]-1β, IL-6, TNF-α), serum soluble TNF receptor concentration (sTNFR I [p55], sTNFR II [p75]), Disease Activity Score in 28 joints (DAS28) and European League of Associations of Rheumatologists (EULAR) improvement criteria.

Safety:

The safety of etanercept was determined using the following assessments: cardiac ultra sonography, chest computed tomography (CT) or X-ray, vital signs, body height and weight, monitoring of Adverse Events (AEs), and laboratory determinations (including anti-etanercept-antibody, and auto antibodies).

Statistical Methods

General Matters for statistical methods were followed:

1. Summary statistics

Summary statistics included the number of patients, mean, standard deviation, median, minimum and maximum

2. Confidence coefficient and its adjustment

The confidence coefficient was decided to be 95%, and no adjustment was considered because the present study was an exploratory study

3. Interim analysis

Interim analysis was not planned in the protocol, however at PMDA request interim analyses were done twice before closing the study.

4. Calculation variables used in analyses

Treatment compliance rate between the consecutive assessment days (%) : 100 x (number of doses) / (specified number of doses between the assessment days **

**: (date of the present assessment - date of the previous assessment) / 7 x 2

Time Window

Baseline: the value at the week 0 that the subjects had been treated as the first TNR-001 study. JRA30%DOI, and change from baselin of JRA core set and other activity endpoints were caluculated with this baseline.

Time window at each evaluation point

Week 0 From 5 days before dosing start date (day 0) of this study

Evaluation points every 4 weeks (n weeks x 7) days -14 days to +13 days after day 0

4 weeks after final dose or early withdrawal 28 days + 14 days after the final dose or early withdrawal

Definition for former studies, shift pattern, and dosing pattern

Definition for former studies, shift pattern, and dosing pattern that initial dose in 207-JA study and change dose during 207-JA were summarized in Table 7-1.

Table 7-1: Definition for former studies, shift pattern, and dosing pattern

Former studies			Shift pattern	Dose pattern	Definition
204	-	-	204→207-JA	0.4 mg continued 0.4 mg decreased	0.4 mg/kg was dosed continuously from 204 Started with 0.4 mg/kg dosing continuosly 204 and decreased dosing at least once during 207-JA
-	-	208-JA	208-JA→207-JA	0.2 mg continued 0.2 mg increased 0.4 mg continued* 0.4 mg decreased*	0.2 mg/kg was dosed continuosly from 208-JA Increased dosing at least once during 207-JA 0.2 mg/kg was dosed at 208-JA and started with 0.4 mg/kg in 207-JA and continued 0.2 mg/kg was dosed at 208-JA and started with 0.4 mg/kg in 207-JA and decreased dosing at least once during 207-JA
204	206-JA (0.4)	-	204→206-JA→207-JA	0.4mg continued 0.4mg decreased	0.4 mg/kg was dosed continuously from 204 Started with 0.4 mg/kg dosing continuosly 204 and decreased dosing at least once during 207-JA
	206-JA (0.2)	-		0.2 mg continued** 0.2 mg increased**	0.4 mg/kg was dosed at 204, 0.2 mg/kg was dosed continuosly from 206-JA 0.4 mg/kg was dosed at 204, 0.2 mg/kg was dosed continuosly from 206-JA and increased dosing at least once during 207-JA

Efficacy Analyses

Summary statistics of JRA core set and other disease activity variables were calculated at each evaluation time point and created the Figures of trend. Also, summary statistics of JRA core set and other disease activity variables were calculated and figured by study shift pattern or by dosing pattern.

Full analysis set

The population of all the subjects who consented to participate in the study from whom the following subjects are excluded: (1) Subjects who violated the GCP (2) Subjects who never received administration of the test article (3) Subjects with no data on the 6 JRA core set variables at baseline, which are required for the calculation of the primary efficacy variable (4) Subjects who have missing data on 3 or more of the 6 JRA core set variables at baseline, which are required for the calculation of the primary efficacy variable, and therefore don't have JRA30% DOI results after administration of the test article.

Per Protocol set

The population of all the subjects who consented to participate in the study from whom the following subjects are excluded: (1) Subjects who are excluded from the FAS (2) Subjects with an important protocoldeviation (3) Subjects with a treatment compliance rate below 80% (4) Subjects in whom none of the primary efficacy variables are adopted as a result of the handling of individual data. (5) Any other subjects who, by decision, were excluded from the PPS at the Case Review Meeting.

Safety Analyses

Safety analysis set was defined as follows:

Safety analysis set

The population of all the subjects who consented to participate in the study from whom the following subjects are excluded: (1) Subjects who violated the GCP (2) Subjects who never received administration of the test article (3) Any other subjects who are decided to be excluded from the safety analysis set at the Case Review Meeting

Demography:

Demographic information for the safety population that comprised all subjects who received at least 1 dose of the test article is presented in Table 8-2. Most subjects (87.5%) were girls. The most frequent age group was 13 to 17 years with 56.3% (n = 18), and the range of their age (median) was 5 to 19 years (14.0 years). The ranges of height and weight (median) were 106.6 to 169.6 cm (147.20 cm) and 17.7 to 75.1 kg (41.05 kg).

The onset types were polyarthritis (87.5%, n = 28), oligoarthritis (9.4%, n = 3), and systemic arthritis (3.1%, n = 1) at the time of obtaining informed consent for the previous studies where subjects had first received TNR-001. At the time of screening for this study, all subjects had polyarthritis as the type of disease. Duration of disease (median) was 5.29 years. Except 1 subject (3.1%) with functional class III, almost all the subjects had good physical function at the start of this study, with functional class I in 19 subjects (59.4%) and class II in 12 subjects

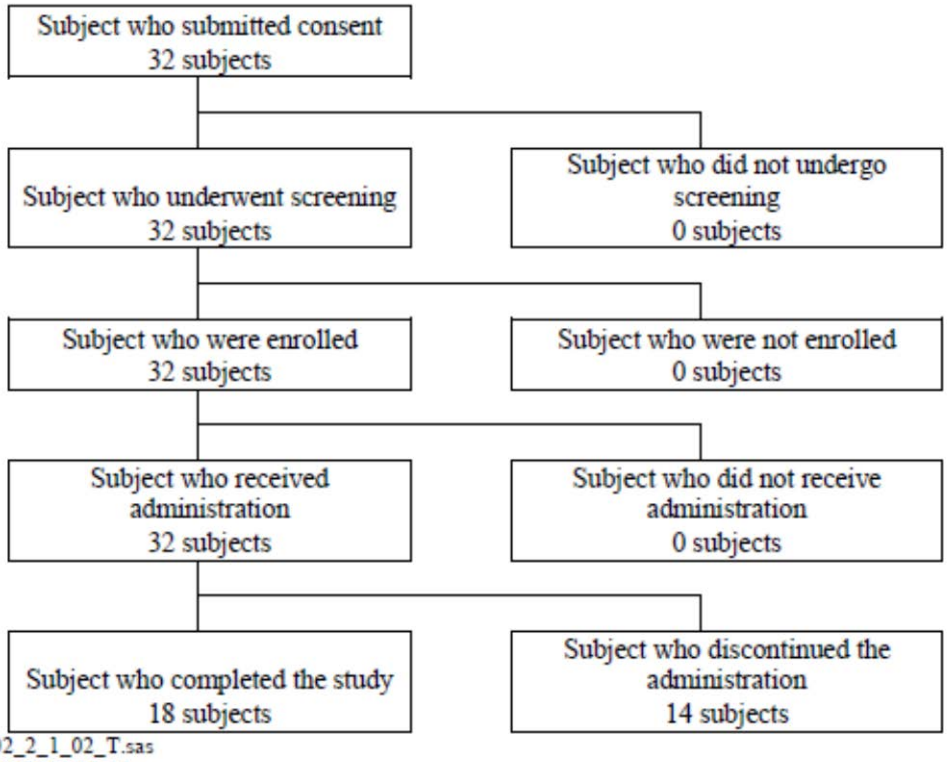
(37.5%). Almost all the subjects (93.8%, n = 30) had complications, and 7 subjects (21.9%) had past medical histories

Results

Recruitment/ Number analysed

A total of 32 subjects with polyarticular juvenile rheumatoid arthritis who had been enrolled in the previous studies (studies 204, 206-JA or 208-JA), had not experienced any safety problems, and were considered to be appropriate for the enrollment into this study by the investigator or subinvestigators were screened, of whom 32 subjects were enrolled. The disposition of subjects is shown in Figure 8-1.

Figure 8-1: Disposition of the subjects (those who submitted consent)



Baseline data

These are summarised in the table below:

Table 8-2 Demographic data (Efficacy Analysis Population)

Parameters (at screening)	Classification	Number of subjects (N = 32)	(%)
Sex	Male	4	(12.5)
	Female	28	(87.5)
Age (years old)	4 - 8	3	(9.4)
	9 - 12	7	(21.9)
	13 - 17	18	(56.3)
	18 -	4	(12.5)
	Mean	13.7	
	Standard deviation	3.6	
	Median	14.0	
	Minimum	5	
	Maximum	19	
Height [a] (cm)	Mean	147.60	
	Standard deviation	15.57	
	Median	147.20	
	Minimum	106.6	
	Maximum	169.6	
Body weight [a] (kg)	Mean	42.71	
	Standard deviation	13.78	
	Median	41.05	
	Minimum	17.7	
	Maximum	75.1	
BSA [a] (m^2)	Mean	1.31	
	Standard deviation	0.28	
	Median	1.29	
	Minimum	0.7	
	Maximum	1.9	
Onset type [b]	Polyarticular	28	(87.5)
	Pauciarticular	3	(9.4)
	Systemic	1	(3.1)
Type of present illness	Polyarthritis	32	(100.0)
	Oligoarthritis	0	(0.0)
	Systemic arthritis	0	(0.0)
Duration of disease (Year)	< 2	3	(9.4)
	2 - 5	12	(37.5)
	5 <	17	(53.1)
	Mean	6.08	
	Standard deviation	3.54	
	Median	5.29	
	Minimum	0.7	
	Maximum	14.3	
Functional classification	Class I	19	(59.4)
	Class II	12	(37.5)
	Class III	1	(3.1)
	Class IV	0	(0.0)
Rheumatoid factor [a]	Negative	12	(37.5)
	Positive	20	(62.5)
Complications	No	2	(6.3)
	Yes	30	(93.8)
Past medical history	No	25	(78.1)
	Yes	7	(21.9)
Drug allergy	No	31	(96.9)
	Yes	1	(3.1)
Enrollment pattern	204 → 207-JA	8	(25.0)
	208-JA → 207-JA	13	(40.6)
	204 → 206-JA → 207-JA	11	(34.4)

a. At baseline
b. At the time of obtaining informed consent for the study where subjects had first received TNR-001

Efficacy results

The baseline values in the previous study where subjects had first received TNR-001, i.e. studies

204, 206-JA, and 208-JA, were regarded as the baseline values for the efficacy evaluation in this study (study 207-JA) . The data at week 0 in this study are also shown for each variable to examine how the efficacy variables observed after the previous studies are changed by the dose changes.

Primary Efficacy Endpoint

JRA core set and other activity assessment measures at each evaluation point are shown in Table 9-3.

Global assessment of disease severity by the physician (median) was 6.00 cm at baseline. It was improved to 0.30 cm at week 0 and ranged from 0.0 to 0.50 cm at week 12 through 216.

Global assessment of overall well-being by the patients or the patient's parent or guardian (median) was 5.0 at baseline. It was improved to 2.0 at week 0 and ranged from 1 to 2 at week 12 through 216.

Number of joints with active disease (median) was 13.0 at baseline. It was reduced to 1.0 at week 0 and then reduced to 0 at week 24 through 216, only except for the score at week 72 was 0.5.

Number of joints with limited motion accompanied by pain or tenderness (median) was 9.5. It was reduced to 0.0 at week 0 and kept 0 through week 216.

CHAQ (median) was 1.125 at baseline and was reduced to 0.188 at week 0. It was well maintained within a range of 0.00 to 0.250 through week 120 and kept 0 through week 216.

ESR (median) was 31.0 mm/hr at baseline. It was reduced to 17.5 mm/hr at week 0 and ranged from 15 to 20.5 mm/hr through week 216.

Assessment of pain level by the subject or the subject's parent or guardian (median) was 5.0 at baseline. It was improved to 2.0 at week 0 and ranged from 1 to 2 at week 12 through 216.

Duration of morning stiffness (median) was 1.00 hr at baseline. It was reduced to 0.00 hr at week 0 and was kept 0.0 hr until week 216.

CRP (median) was 1.850 mg/dL at baseline. It was reduced to 0.060 mg/dL at week 0 and ranged from 0.02 to 0.10 mg/dL at week 12 through 216. It was increased to 0.84 mg/dL at week 216.

Rheumatoid factor (median) was 71.5 IU/mL at baseline. It was improved to 51.0 IU/mL at week 0 and ranged from 8 to 45.5 IU/mL at week 24 through 216.

Thus, the improvements in the following objective measures observed after the previous study were maintained until week 216 in this study: 4 measures in JRA core set (global assessment of disease severity by the physician, number of joints with active disease, number of joints with limited motion accompanied by pain or tenderness, and ESR), duration of early morning stiffness, CRP, and rheumatoid factor. The improvements in the following subjective measures seen after the previous study were also maintained through the study period: 2 measures in JRA core set (global assessment of overall well-being by the subject or the subject's parent or guardian and CHAQ) and assessment of pain level by the subject or the subject's parent or guardian.

Table 9-3 Changes in JRA core set and other activity endpoints (Efficacy Analysis Population)

Parameters	Evaluation point	No. of subjects	Mean	SD	Median	Min.	Max.
JRA core set							
Physician Global Assessment (cm)	Baseline	32	6.08	1.82	6.00	0.1	9.5
	Week 0	32	1.03	1.86	0.30	0.0	9.5
	Week 12	32	1.47	2.25	0.50	0.0	9.0
	Week 24	31	1.00	1.66	0.5	0.0	6.7
	Week 36	31	0.53	0.72	0.3	0.0	3.2
	Week 48	28	0.47	0.60	0.25	0.0	2.1
	Week 72	28	0.52	0.80	0.10	0.0	3.6
	Week 96	27	0.57	1.59	0.0	0.0	8.1
	Week 120	26	0.67	1.17	0.15	0.0	4.8
	Week 144	26	0.71	1.47	0.20	0.0	7.3
	Week 168	20	0.53	0.89	0.15	0.0	3.6
	Week 192	19	0.57	0.81	0.1	0.0	2.6
	Week 216	2	0.05	0.07	0.05	0.0	0.1
Patients or guardians Global Assessment	Baseline	32	5.3	2.1	5.0	1	9
	Week 0	32	2.4	1.9	2.0	0	9
	Week 12	32	2.2	2.4	2.0	0	9
	Week 24	31	2.3	2.3	2	0	9
	Week 36	31	1.8	1.9	1	0	8
	Week 48	28	2.0	2.1	2.0	0	9
	Week 72	28	1.8	2.0	1.0	0	9
	Week 96	27	1.6	1.8	1	0	7
	Week 120	26	1.6	1.6	1.0	0	6
	Week 144	26	1.7	2.0	1.0	0	8
	Week 168	20	2.0	2.1	1.0	0	7
	Week 192	19	1.8	1.7	2	0	6
	Week 216	3	1.3	1.2	2	0	2
Number of active joints (counts)	Baseline	32	19.0	15.0	13.0	5	66
	Week 0	32	3.0	5.7	1.0	0	28
	Week 12	32	4.3	9.6	1.0	0	50
	Week 24	31	2.7	6.3	0	0	30
	Week 36	31	1.9	4.9	0	0	26
	Week 48	28	1.0	1.6	0.0	0	6
	Week 72	28	0.6	0.8	0.5	0	3
	Week 96	27	0.9	1.6	0	0	7
	Week 120	26	0.9	1.8	0.0	0	8
	Week 144	26	0.8	1.9	0.0	0	7
	Week 168	20	1.4	3.0	0.0	0	12
	Week 192	19	1.4	4.0	0	0	17
	Week 216	3	1.0	1.7	0	0	3

Number of joints with limited motion with pain or tenderness (Counts)	Baseline	32	14.4	13.5	9.5	3	64
	Week 0	32	0.9	3.1	0.0	0	16
	Week 12	32	2.9	9.1	0.0	0	50
	Week 24	31	1.4	4.3	0	0	20
	Week 36	31	1.0	4.7	0	0	26
	Week 48	28	0.2	0.4	0.0	0	1
	Week 72	28	0.1	0.4	0.0	0	1
	Week 96	27	0.3	1.0	0	0	5
	Week 120	26	0.2	0.5	0.0	0	2
	Week 144	26	0.2	0.8	0.0	0	4
	Week 168	20	0.2	0.4	0.0	0	1
	Week 192	19	0.1	0.2	0	0	1
	Week 216	3	1.0	1.7	0	0	3
CHAQ	Baseline	32	1.207	0.906	1.125	0.00	3.00
	Week 0	32	0.492	0.620	0.188	0.00	2.38
	Week 12	32	0.512	0.693	0.250	0.00	2.50
	Week 24	31	0.476	0.615	0.13	0.00	2.38
	Week 36	31	0.399	0.574	0.13	0.00	2.50
	Week 48	28	0.429	0.589	0.188	0.00	2.50
	Week 72	28	0.375	0.575	0.125	0.00	2.38
	Week 96	27	0.347	0.627	0.13	0.00	2.88
	Week 120	26	0.264	0.555	0.000	0.00	2.50
	Week 144	26	0.269	0.492	0.000	0.00	2.13
	Week 168	20	0.213	0.391	0.000	0.00	1.25
	Week 192	19	0.217	0.365	0.00	0.00	1.00
	Week 216	3	0.000	0.000	0.00	0.00	0.00
ESR (mm/hr)	Baseline	32	38.7	27.7	31.0	4	109
	Week 0	32	26.6	27.8	17.5	4	126
	Week 12	32	24.4	25.3	16.0	3	126
	Week 24	31	21.4	15.6	19	1	74
	Week 36	31	19.6	16.1	16	1	62
	Week 48	28	21.5	14.2	20.5	1	54
	Week 72	28	19.9	14.4	17.5	1	50
	Week 96	25	18.7	13.5	18	1	47
	Week 120	26	17.7	14.2	15.0	1	52
	Week 144	24	21.2	18.2	18.0	1	67
	Week 168	20	15.4	10.5	15.0	0	42
	Week 192	19	16.5	11.8	15	1	44
	Week 216	3	28.7	31.0	16	6	64
Pain score by subjects or guardians	Baseline	32	5.5	2.4	5.0	0	10
	Week 0	32	2.4	2.1	2.0	0	9
	Week 12	32	2.3	2.4	2.0	0	8
	Week 24	31	2.7	2.8	2	0	10
	Week 36	31	2.1	2.4	1	0	9
	Week 48	28	2.3	2.4	2.0	0	9
	Week 72	28	1.9	2.2	1.0	0	9
	Week 96	27	1.9	2.1	1	0	8
	Week 120	26	1.5	1.8	1.0	0	7
	Week 144	26	2.1	2.3	1.0	0	8
	Week 168	20	2.0	1.9	1.5	0	6
	Week 192	19	1.9	1.9	2	0	6
	Week 216	3	1.3	1.2	2	0	2

Duration of morning stiffness (hours)	Baseline	32	1.53	1.46	1.00	0.0	5.0
	Week 0	32	0.30	0.60	0.00	0.0	2.0
	Week 12	31	0.63	1.38	0.0	0.0	6.0
	Week 24	31	0.45	1.08	0.0	0.0	5.5
	Week 36	31	0.21	0.58	0.0	0.0	3.0
	Week 48	28	0.25	0.65	0.00	0.0	3.0
	Week 72	28	0.43	1.09	0.00	0.0	4.0
	Week 96	27	0.26	0.64	0.0	0.0	2.0
	Week 120	26	0.46	1.26	0.00	0.0	5.0
	Week 144	26	0.11	0.24	0.00	0.0	1.0
	Week 168	20	0.18	0.49	0.00	0.0	2.0
	Week 192	19	0.21	0.51	0.0	0.0	2.0
	Week 216	3	0.17	0.29	0.0	0.0	0.5
CRP (mg/dL)	Baseline	32	2.223	2.309	1.850	0.02	7.73
	Week 0	32	0.846	1.836	0.060	0.02	7.82
	Week 12	31	0.585	0.905	0.08	0.02	3.63
	Week 24	31	0.632	1.083	0.07	0.02	3.52
	Week 36	30	0.593	0.968	0.065	0.02	3.33
	Week 48	28	0.856	1.458	0.100	0.02	5.69
	Week 72	28	0.585	1.113	0.060	0.02	5.56
	Week 96	27	0.330	0.505	0.06	0.02	1.68
	Week 120	26	0.403	0.906	0.030	0.02	3.71
	Week 144	26	0.502	0.876	0.035	0.02	2.88
	Week 168	20	0.282	0.567	0.045	0.02	2.48
	Week 192	19	0.353	0.724	0.02	0.02	2.72
	Week 216	3	0.980	1.037	0.84	0.02	2.08
Rheumatoid factor (IU/mL)	Baseline	32	427.4	1616.2	71.5	0	9200
	Week 0	32	509.7	1897.5	51.0	1	10800
	Week 24	32	457.2	1396.7	45.5	1	7800
	Week 48	30	367.1	959.0	44.0	1	5100
	Week 72	28	370.4	881.9	45.0	1	4400
	Week 96	27	355.5	1004.4	43	1	5200
	Week 120	26	427.1	1575.7	33.0	1	8100
	Week 144	26	377.6	1323.1	34.5	1	6800
	Week 168	20	110.6	141.1	39.0	1	390
	Week 192	19	111.4	141.0	37	1	395
	Week 216	3	16.3	20.8	8	1	40

The baseline values in the previous study where subjects had first received TNR-001 were regarded as the baseline values in this study.
Protocol No.:0881A1-207-JA
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Of 8 subjects who were enrolled directly from 204, 3 subject were withdrawn at week 32, 39, and 138, and the other subjects completed the study and treated for 184 to 204 weeks. Generally all subjects maintained the improvement of JRA core set and other activity observed at week 0 of 207-JA until the final evaluation for each subject, except rheumatoid factor.

Of 12 subjects treated at 0.2 mg/kg in the studies 208-JA and 207-JA, 4 subjects maintained the improvements at week 0 of 207-JA till the final evaluation of 207-JA in all variables except rheumatoid factor. Of the 4 subject, 1 subject was discontinued at week 170.

Of 12 subjects completed 208-JA, 8 subjects showed signs of JRA activation during this study, then these 8 subjects received an increased dose of 0.4 mg/kg (at 11w, 13w (2 subjects), 14w, 25w (2 subjects), 29w, and 30w respectively) because of “criteria for dose increase or treatment discontinuation,” and maintained the improvements seen after the study 208-JA till week 192. Of the 8 subjects, 4 were discontinued at week 93, 125, 131, and 145.

One (1) subject (A925-9603-101) who completed 208-JA and increased the dose to 0.4 mg/kg in 207-JA was discontinued due to insufficient efficacy. Although the subject showed the improvement in the number of active joints (improved from 29 to 21), the number of joints with limited motion accompanied by pain or tenderness (from 18 to 15), CRP (from 6.820 to 2.300 mg/dL), and rheumatoid factor (from 390.0 to 310.0 IU/mL), no improvement was observed in all the other JRA core set and other activities. The subject was discontinued on the first day in week 8 due to “no efficacy”.

In 6 subjects treated at 0.4 mg/kg in the studies 204, 206-JA and 207-JA, 3 were discontinued the study because of the subject refusal at week 71, 138, and 175. Three (3) subjects completed the study and treated for 171 to 172 weeks. Four (4) subjects of whose data were available at week 168, the improvements seen at week 0 of 207-JA were maintained in all variables except rheumatoid factor.
Of 5 subjects treated at 0.4 mg/kg in the study 204 and 0.2 mg/kg in the studies 206-JA and 207-JA, 2 subjects maintained the improvements seen after the previous studies till week 144 in this study. Of the 2 subjects, 1 subject was discontinued from the study because of subject refusal. Three (3) subjects who treated 204, 206-JA (at 0.2 mg/kg) and 207-JA showed signs of JRA

activation during this study (week 0 and week 12 to 24). Thus, these 3 subjects received an increased dose of 0.4 mg/kg (at 9w, 10w, and14w respectively) because they have met the "criteria for dose increase or treatment discontinuation ". One subject was discontinued at week 33 because of subject refusal. The other 2 subjects maintained the improvements at week 0 of 207-JA till week 144).
Overall, despite the small number of samples, the analyses by pattern of enrollment into the studies and pattern of dosing indicated that subjects who received the same dose of 0.4 mg/kg as the previous studies well maintained the improvements observed after the previous studies during this study. On the other hand, 11 subjects (64.7%) out of 17 who received the same dose of 0.2 mg/kg as the previous studies failed to achieve control of signs and symptoms but they received the increased dose of 0.4 mg/kg during week 0 to 48 and showed improvement.

Secondary Efficacy Endpoints

JRA30%DOI, JRA50%DOI, and JRA70%DOI

The JRA30%DOI (two-sided 95% confidence intervals) were 96.9% (83.8% to 99.9%) at week 0, and 90.6% to 100% at week 12 through 216.
The JRA 50% DOI (95% two-sided confidence intervals) were 93.8% (79.2% to 99.2%) at week 0, and 90.3% to 100% at week 12 through 216.
The JRA 70% DOI (95% two-sided confidence intervals) were 84.4%(67.2% to 94.7%) at week 0 , and 66.7% to 100.0% at week 12 through 216.
The response rates of JRA30%DOI, JRA50%DOI, and JRA70%DOI were significantly improved at any evaluation points until week 216.

In the analyses by enrollment pattern and administration pattern into the studies ,one (1) subject who was discontinued from the study 208-JA due to insufficient efficacy and enrolled in 207-JA with dose 0.4 mg/kg showed no improvement in the JRA DOIs. Of 12 subjects treated at 0.2 mg/kg in the studies 208-JA and 207-JA, 8 subjects showed reduction of JRA DOIs during the first 24 weeks and increased the JRA DOIs after week 36 because most of the subject increased the dose to 0.4 mg/kg. Except for these subjects, in general, there was no effect of the pattern of enrollment into the studies and the pattern of dosing on the JRA DOIs, although the sample size was small in the analyses by these patterns.
Significant improvements were found at each evaluation point through the study period in all

measures except rheumatoid factor and ESR: the improvement rates (median) were 90.59% to 100.0% in the physicians global assessment, 50.0% to 79.17% in the subjects or guardians global assessment, 92.06% to 100.0% in the number of active joints, 100.0% in the number of joints with limited motion with pain or tenderness, 61.90% to 100.0% in CHAQ, 40.4% to 68.27% in ESR, 60.00 to 83.3% in the pain score by the patients or guardian, 93.8% to 100.0% in the duration of morning stiffness, and 63.6% to 94.65% in CRP.

The results for the secondary endpoints (JIA 30% DOI, JIA 50% DOI and JIA 70% DOI, improvement rates of JIA core set and other activity assessment measures, drug characteristics and effect of subject characteristics, and evaluation of efficacy by dose), and the other endpoints (cytokines and DAS28) also indicated that the improvement observed after the previous studies were well maintained through Week 48. The analyses by pattern of enrolment into the studies and pattern of dosing showed that all subjects who received the same dose of 0.4 mg/kg as the previous studies well maintained the improvements observed after the previous studies throughout the study period, with exception of 1 subject treated at0.4 mg/kg from Study 0881A1-208-JA. On the other hand, 11 subjects (64.7%) out of 17 subjects who received the same dose of 0.2 mg/kg as the previous studies showed no improvement in these endpoints but obtained improvement after receiving an increased dose of 0.4 mg/kg, indicating that a dose of 0.2 mg/kg may be less efficacious.

Evaluation of Efficacy by Dose

Of 17 subjects who received 0.2 mg/kg as the first dose, 11 subjects changed their dose to 0.4 mg/kg; 3 subjects by Week 12, 4 subjects during Weeks 12 through 24, and 4 subjects during Weeks 24 through 36. No subjects changed their dose after Week 36. Juvenile idiopathic arthritis core set and other activity assessment measures maintained improvement after Week 36.

None of 15 subjects whose initial dose in this study was 0.4 mg/kg had their dose decreased. Evaluation of JIA core set and other activity measures at each evaluation point until Week 48 by dose showed that the improvements in all measures seen at Week 0 were well maintained through the study period in the both dose groups, except that there were no improvements in rheumatoid factor in the 0.2 mg/kg group.

Other Analyses

Change in Cytokine Level with Times

There was no change in the median serum IL-1β concentration at each evaluation point until week 48. The median serum IL-6 level ranged from 1.40 to 2.50 pg/mL and was within a reference range (below 4.0 pg/mL), with the improvement rate (median) of 79.09% to 82.45 %. Although the median serum TNF-α concentration was increased than that at baseline in the previous studies, almost no change in the median serum TNF-α concentration was observed during weeks 0 to 48 in this study. In the evaluation for the soluble TNF receptors, there was almost no change in the median serum sTNFRI (p55) level. The median serum sTNFRII (p75) concentration was clearly increased at week 0 and the increased level was maintained till week 48.

DAS28

DAS28 was additionally assessed using the actually observed data, because DAS28 represents a disease activity of JRA at an evaluation point as an absolute value and is suitable to assess the effect of treatment on symptoms. Assessment by EULAR improvement criteria, which was based on DAS28, was also conducted.

Overall, the DAS28 (median) indicated low disease activity (DAS28<3.2) at any evaluation points through the study period. Despite small number of samples, the analyses by pattern of enrollment into the studies and pattern of dosing showed that all subjects who received the same dose of 0.4 mg/kg as the previous studies well maintained the improvements observed after the previous studies during this study, with exception of 1 subject treated at 0.4 mg/kg in the studies 208-JA and 207-JA.

On the other hand, 11 (64.7%) of 17 subjects who received the same dose of 0.2 mg/kg as the previous studies showed increased DAS28 scores but obtained improvement after receiving an increased dose of 0.4 mg/kg, indicating that a dose of 0.2 mg/kg might be ineffective.

Safety results

Extent of Exposure

All of 32 subjects were included in the safety analysis.

Drug-taking rates and applied doses of the study drug

The administration rate (mean ± SD) between the first and last day of study treatment was high at 97.38 ± 4.14%, with a dosage (mean±SD) of 15.47±5.59 mg.

Duration of exposure to the study drug

14 subjects discontinued the study and 18 subjects completed the study.

Incidence of adverse events and adverse drug reactions

Incidences of all AEs and related AEs are presented in Table 10-2

In total, 356 AEs were reported from 32 subjects (100.0%): 99 infections from 31 subjects (96.9%), 18 laboratory abnormalities from 10 subjects (31.3%), 9 injection site reactions from 9subjects (28.1%) and 230 other adverse events from 31 subjects (96.9%). Any subject had at least one event of adverse event and was highly likely to have infection.

Summarization of AEs by severity revealed that any event was categorized in grade 1 or 2 with exception of 2 events of cataract, 1 event each of campylobacter gastroenteritis, subcutaneous abscess, cellulitis, back pain, and feeling abnormal in grade 3 and no cases of grade 4 were observed.

Overall, 275 related adverse events were reported from 31 subjects (96.9%): 98 infections from 31 subjects (96.9%), 18 laboratory abnormalities in 10 subjects (31.3%), 9 injection site reactions from 9 subjects (28.1%) and 150 other AEs from 30 subjects (93.8%). Ninety percent (90%) or more of the subjects had related AEs, and any one of them had infection as a related AE.

Summarization of related AEs by severity revealed that any event was categorized into grade 1 or 2 with exception of 1 each of campylobacter gastroenteritis, subcutaneous abscess, cellulitis, and back pain in grade 3.

Table 10-2 Incidences of adverse events and adverse drug reactions (Safety Analysis Population)

All adverse events — Number of subjects, number of events (%)

		All (N = 32)	Infections (N = 32)	Injection site reaction (N = 32)	Laboratory abnormalities (N = 32)	Other AEs [c] (N = 32)
Number of subjects occurred AEs (%)		32 (100.0)	31 (96.9)	9 (28.1)	10 (31.3)	31 (96.9)
95% confidence interval		89.1 - 100.0	83.8 - 99.9	13.7 - 46.7	16.1 - 50.0	83.8 - 99.9
Number of events [a]		356	99	9	18	230
Grade [b]	1	1	1	3	7	2
	2	25	27	6	3	25
	3	6	3	0	0	4
	4	0	0	0	0	0

Related adverse events

		All (N = 32)	Infections (N = 32)	Injection site reactions (N = 32)	Laboratory abnormalities (N = 32)	Other AEs [c] (N = 32)
Number of subjects occurred ADRs (%)		31 (96.9)	31 (96.9)	9 (28.1)	10 (31.3)	30 (93.8)
95% confidence interval		83.8 - 99.9	83.8 - 99.9	13.7 - 46.7	16.1 - 50.0	79.2 - 99.2
Number of events [a]		275	98	9	18	150
Grade [b]	1	0	1	3	7	2
	2	28	27	6	3	27
	3	3	3	0	0	1
	4	0	0	0	0	0

a. It was counted as one event when the same symptom developed in the same subject for more than once
b. The one with the highest grade among all adverse events developed in each subject
c. Any events other than infections, administration site reaction, or abnormal changes in laboratory findings
All AEs: "definitely related", "probably related", "possibly related", or "not related"
Related AEs: "definitely related", "probably related", or "possibly related"

Adverse events

These are summarised in Table 10.3

The most frequent other AEs (≥2 subjects) included headache (12 subjects, 37.5%), rash (10 subjects, 31.3%), abdominal pain, joint sprain, contusion, and arthropod sting (8 subjects, 25.0%), injection site haemorrhage (7 subjects, 21.9%), myalgia (6 subjects, 18.8%), diarrhoea and constipation (5 subjects, 15.6%), conjunctivitis allergic, rhinitis allergic, epistaxis, and chest pain (4 subjects, 12.5%), nausea, gastritis, stomach discomfort, stomatitis, ganglion, hypoaesthesia, eczema, and urticaria (3 subjects, 9.4%), uveitis, asthenopia, cataract, arthralgia, musculoskeletal stiffness, shoulder pain, pain in extremity, toe deformity, rhinorrhoea, injury corneal, excoriation, foot fracture, injury, chillblains, thermal burn, back injury, menstruation irregular, hernia, chest discomfort, malaise, alopecia, seasonal allergy, and weight decreased (2 subjects, 6.3%).

The most frequent related other AEs (≥2 subjects) included headache (10 subjects, 31.3%), rash (9 subjects, 28.1%), abdominal pain (8 subjects, 25.0%), diarrhoea and constipation (5 subjects, 15.6%), rhinitis allergic, and chest pain (4 subjects, 12.5%), arthropod sting, epistaxis, conjunctivitis allergic, gastritis, stomach discomfort, stomatitis, ganglion, eczema, and urticaria (3 subjects, 9.4%), hypoaesthesia, myalgia, uveitis, asthenopia, arthralgia, toe deformity, rhinorrhoea, chillblains, hernia, malaise, alopecia, and seasonal allergy (2 subjects, 6.3%).
As for all other AEs, 2 subjects of grade 1, 25 subjects of grade 2 and 4 subject of grade 3, and

no subjects of grade 4 were observed. As for related other AEs, 2 subjects of grade 1, 27 subjects of grade 2 and 1 subject of grade 3, and no subjects of grade 4 were observed.

Table 10-3 Incidences of adverse events and adverse drug reactions (Safety Analysis Population)

SOC	PT	Number of subjects reporting AEs (%) (N = 32)	Number of subjects reporting related AEs (%) (N = 32)
< Infections >			
Total		31 (96.9)	31 (96.9)
Gastrointestinal disorders		2 (6.3)	2 (6.3)
	Pericoronitis	2 (6.3)	2 (6.3)
Infections and infestations		31 (96.9)	31 (96.9)
	Influenza	7 (21.9)	7 (21.9)
	Gastroenteritis viral	2 (6.3)	2 (6.3)
	Bronchitis viral	1 (3.1)	1 (3.1)
	Viral upper respiratory tract infection	1 (3.1)	1 (3.1)
	Campylobacter gastroenteritis	1 (3.1)	1 (3.1)
	Tracheobronchitis mycoplasmal	1 (3.1)	1 (3.1)
	Pneumonia mycoplasmal	1 (3.1)	1 (3.1)
	Gastroenteritis	6 (18.8)	6 (18.8)
	Pharyngitis	6 (18.8)	6 (18.8)
	Purulence	2 (6.3)	2 (6.3)
	Bronchitis	3 (9.4)	3 (9.4)
	Bronchitis acute	1 (3.1)	1 (3.1)
	Oral candidiasis	1 (3.1)	1 (3.1)
	Upper respiratory tract infection	10 (31.3)	10 (31.3)
	Herpes zoster	3 (9.4)	3 (9.4)
	Herpes simplex	1 (3.1)	1 (3.1)
	Otitis media	1 (3.1)	1 (3.1)
	Nail tinea	1 (3.1)	1 (3.1)
	Urinary tract infection	2 (6.3)	2 (6.3)
	Impetigo	1 (3.1)	1 (3.1)
	Hordeolum	2 (6.3)	2 (6.3)
	Subcutaneous abscess	2 (6.3)	2 (6.3)
	Skin candida	1 (3.1)	1 (3.1)
	Nasopharyngitis	29 (90.6)	29 (90.6)

	Cellulitis	1 (3.1)	1 (3.1)
	Tonsillitis	2 (6.3)	2 (6.3)
	Tinea versicolour	1 (3.1)	1 (3.1)
	Dental caries	4 (12.5)	3 (9.4)
Blood and lymphatic system disorders		1 (3.1)	1 (3.1)
	Lymphadenitis	1 (3.1)	1 (3.1)
Respiratory, thoracic and mediastinal disorders		1 (3.1)	1 (3.1)
	Cough	1 (3.1)	1 (3.1)
Skin and subcutaneous tissue disorders		1 (3.1)	1 (3.1)
	Rash	1 (3.1)	1 (3.1)
< Injection site reactions >			
Total		9 (28.1)	9 (28.1)
General disorders and administration site conditions		9 (28.1)	9 (28.1)
	Injection site reaction	9 (28.1)	9 (28.1)
< Laboratory abnormalities >			
Total		10 (31.3)	10 (31.3)
Renal and urinary disorders		1 (3.1)	1 (3.1)
	Haematuria	1 (3.1)	1 (3.1)
Investigations		9 (28.1)	9 (28.1)
	Haematocrit decreased	1 (3.1)	1 (3.1)
	Haemoglobin decreased	2 (6.3)	2 (6.3)
	Lymphocyte count increased	1 (3.1)	1 (3.1)
	Platelet count increased	1 (3.1)	1 (3.1)
	Blood creatine phosphokinase increased	1 (3.1)	1 (3.1)
	Blood urea increased	2 (6.3)	2 (6.3)
	Eosinophil count increased	1 (3.1)	1 (3.1)
	Red blood cell count decreased	1 (3.1)	1 (3.1)
	Bacteria urine	1 (3.1)	1 (3.1)
	White blood cells urine positive	1 (3.1)	1 (3.1)
	White blood cell count increased	4 (12.5)	4 (12.5)
	Granulocyte count decreased	1 (3.1)	1 (3.1)
< Others >			
Total		31 (96.9)	30 (93.8)
Gastrointestinal disorders		18 (56.3)	18 (56.3)
	Nausea	3 (9.4)	0 (0.0)
	Gastritis	3 (9.4)	3 (9.4)
	Gastric ulcer	1 (3.1)	1 (3.1)
	Stomach discomfort	3 (9.4)	3 (9.4)
	Diarrhoea	5 (15.6)	5 (15.6)
	Cheilitis	1 (3.1)	1 (3.1)
	Stomatitis	3 (9.4)	3 (9.4)
	Toothache	1 (3.1)	1 (3.1)
	Abdominal pain upper	1 (3.1)	1 (3.1)
	Abdominal pain	8 (25.0)	8 (25.0)
	Abdominal discomfort	1 (3.1)	0 (0.0)
	Constipation	5 (15.6)	5 (15.6)
	Vomiting	1 (3.1)	1 (3.1)
Infections and infestations		2 (6.3)	2 (6.3)
	Gastroenteritis	1 (3.1)	1 (3.1)
	Rhinitis	1 (3.1)	1 (3.1)

Eye disorders		12 (37.5)	10 (31.3)
	Conjunctivitis allergic	4 (12.5)	3 (9.4)
	Uveitis	2 (6.3)	2 (6.3)
	Eye pruritus	1 (3.1)	1 (3.1)
	Ocular hyperaemia	1 (3.1)	0 (0.0)
	Asthenopia	2 (6.3)	2 (6.3)
	Conjunctivitis	1 (3.1)	1 (3.1)
	Papilloedema	1 (3.1)	1 (3.1)
	Iritis	1 (3.1)	1 (3.1)
	Cataract	2 (6.3)	0 (0.0)
	Glaucoma	1 (3.1)	1 (3.1)
	Chalazion	1 (3.1)	1 (3.1)
Musculoskeletal and connective tissue disorders		16 (50.0)	13 (40.6)
	Ganglion	3 (9.4)	3 (9.4)
	Temporomandibular joint syndrome	1 (3.1)	1 (3.1)
	Bursitis	1 (3.1)	1 (3.1)
	Periarthritis	1 (3.1)	0 (0.0)
	Arthralgia	2 (6.3)	2 (6.3)
	Musculoskeletal stiffness	2 (6.3)	1 (3.1)
	Myalgia	6 (18.8)	2 (6.3)
	Muscle spasms	1 (3.1)	1 (3.1)
	Shoulder pain	2 (6.3)	0 (0.0)
	Pain in extremity	2 (6.3)	0 (0.0)
	Limb discomfort	1 (3.1)	1 (3.1)
	Spondylolysis	1 (3.1)	1 (3.1)
	Back pain	1 (3.1)	1 (3.1)
	Tenosynovitis	1 (3.1)	1 (3.1)
	Toe deformity	2 (6.3)	2 (6.3)
Blood and lymphatic system disorders		2 (6.3)	2 (6.3)
	Iron deficiency anaemia	1 (3.1)	1 (3.1)
	Anaemia	1 (3.1)	1 (3.1)
Vascular disorders		1 (3.1)	0 (0.0)
	Pallor	1 (3.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		10 (31.3)	10 (31.3)
	Allergic bronchitis	1 (3.1)	1 (3.1)
	Rhinitis allergic	4 (12.5)	4 (12.5)
	Vocal cord polyp	1 (3.1)	1 (3.1)
	Epistaxis	4 (12.5)	3 (9.4)
	Rhinorrhoea	2 (6.3)	2 (6.3)
	Asthma	1 (3.1)	1 (3.1)
	Tonsillar hypertrophy	1 (3.1)	1 (3.1)
Social circumstances		1 (3.1)	0 (0.0)
	Tanning	1 (3.1)	0 (0.0)
Injury, poisoning and procedural complications		25 (78.1)	8 (25.0)
	Injury corneal	2 (6.3)	1 (3.1)
	Joint sprain	8 (25.0)	0 (0.0)
	Neck injury	1 (3.1)	0 (0.0)
	Contusion	8 (25.0)	0 (0.0)
	Excoriation	2 (6.3)	0 (0.0)
	Arthropod sting	8 (25.0)	3 (9.4)

	Foot fracture	2 (6.3)	1 (3.1)
	Injury	2 (6.3)	1 (3.1)
	Chillblains	2 (6.3)	2 (6.3)
	Cephalhaematoma	1 (3.1)	0 (0.0)
	Heat stroke	1 (3.1)	0 (0.0)
	Thermal burn	2 (6.3)	0 (0.0)
	Back injury	2 (6.3)	0 (0.0)
Nervous system disorders		15 (46.9)	12 (37.5)
	Hypoaesthesia	3 (9.4)	2 (6.3)
	Carpal tunnel syndrome	1 (3.1)	1 (3.1)
	Tremor	1 (3.1)	0 (0.0)
	Dizziness postural	1 (3.1)	1 (3.1)
	Headache	12 (37.5)	10 (31.3)
	Cerebral infarction	1 (3.1)	1 (3.1)
	Migraine	1 (3.1)	1 (3.1)
Reproductive system and breast disorders		4 (12.5)	3 (9.4)
	Dysmenorrhoea	1 (3.1)	1 (3.1)
	Hypertrophy breast	1 (3.1)	1 (3.1)
	Menstruation irregular	2 (6.3)	1 (3.1)
Psychiatric disorders		2 (6.3)	0 (0.0)
	Depression	1 (3.1)	0 (0.0)
	Insomnia	1 (3.1)	0 (0.0)
Congenital, familial and genetic disorders		1 (3.1)	0 (0.0)
	Talipes	1 (3.1)	0 (0.0)
General disorders and administration site conditions		18 (56.3)	13 (40.6)
	Hernia	2 (6.3)	2 (6.3)
	Feeling abnormal	1 (3.1)	0 (0.0)
	Face oedema	1 (3.1)	1 (3.1)
	Chest pain	4 (12.5)	4 (12.5)
	Chest discomfort	2 (6.3)	1 (3.1)
	Malaise	2 (6.3)	2 (6.3)
	Injection site haemorrhage	7 (21.9)	1 (3.1)
	Injection site pain	1 (3.1)	0 (0.0)
	Application site oedema	1 (3.1)	0 (0.0)
	Cyst	1 (3.1)	0 (0.0)
	Fatigue	1 (3.1)	1 (3.1)
	Oedema	1 (3.1)	1 (3.1)
	Pain	1 (3.1)	1 (3.1)
Metabolism and nutrition disorders		1 (3.1)	1 (3.1)
	Anorexia	1 (3.1)	1 (3.1)
Skin and subcutaneous tissue disorders		17 (53.1)	14 (43.8)
	Acne	1 (3.1)	0 (0.0)
	Pruritus	1 (3.1)	1 (3.1)
	Dermatitis atopic	1 (3.1)	1 (3.1)
	Hyperkeratosis	1 (3.1)	0 (0.0)
	Erythema	1 (3.1)	1 (3.1)
	Eczema	3 (9.4)	3 (9.4)
	Palmar erythema	1 (3.1)	0 (0.0)
	Alopecia	2 (6.3)	2 (6.3)
	Rash	10 (31.3)	9 (28.1)

	Haemorrhage subcutaneous	1 (3.1)	0 (0.0)
	Dermatitis	1 (3.1)	1 (3.1)
	Skin fissures	1 (3.1)	0 (0.0)
	Skin ulcer	1 (3.1)	1 (3.1)
	Prurigo	1 (3.1)	1 (3.1)
	Urticaria	3 (9.4)	3 (9.4)
Immune system disorders		2 (6.3)	2 (6.3)
	Seasonal allergy	2 (6.3)	2 (6.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1 (3.1)	1 (3.1)
	Hair follicle tumour benign	1 (3.1)	1 (3.1)
Investigations		4 (12.5)	3 (9.4)
	Blood pressure increased	1 (3.1)	1 (3.1)
	Weight decreased	2 (6.3)	1 (3.1)
	Weight increased	1 (3.1)	1 (3.1)

SOC: System Organ Class, PT: Preferred Term

In this study, doses could be changed according to the subject's condition which was permitted and 11 out of 17 subjects, who were treated with 0.2 mg/kg as the initial dose, received an increased dose of 0.4 mg/kg during the study.

There were no differences in severity of AEs reported in subjects receiving 0.2 mg/kg versus 0.4 mg/kg as the initial dosage. Also, there was no difference in the occurrence of AEs among subgroup, such as by age, by onset disease types and by study transition patterns.

Laboratory test abnormality

The most frequent laboratory abnormalities (≥2 subjects) included white blood cell count increased (4 subjects, 12.5%), haemoglobin decreased and blood urea increased (2 subjects, 6.3%). All laboratory abnormalities were considered to be related to the test articles.
As for all laboratory abnormalities, 7 subjects of grade 1 and 3 subjects of grade 2, and no subjects of grade 3 or 4 were observed. Laboratory values (median) showed no clinically unfavorable changes.

Deaths

No subjects died during this study.

Serious Adverse Events

Serious adverse events reported in this study consisted of 1 subject of cellulitis (study 206-JA [0.4 mg/kg] →study 207-JA [0.4 mg/kg continued]), 2 subjects of cataract (study 204 → study 207-JA [0.4 mg/kg continued] and 208-JA → study 207-JA [0.2 mg/kg continued], each 1 subject), 1 subject of feeling abnormal (study 208-JA → study 207-JA [0.2 mg/kg increased]) and 1 subject of back pain and campylobacter gastroenteritis (study 206-JA [0.2 mg/kg] → study 207-JA [0.2 mg/kg continued], 1 subject). All the events were considered "not related" to the test article with the exception that cellulitis, back pain, campylobacter gastroenteritis and subcutaneous abscess were considered "possibly related" to the drug.

Safety-Related Discontinuations

Two subjects were discontinued from the study because of SAEs.

Autoantibody values

Anti-Sm antibodies, anti-SS-B/La antibodies and anti-RNP antibodies were negative in all the subjects. Among 5 subjects of positive anticardiolipin antibodies, 2 subjects showed positive inversion during the study. Among 28 subjects of positive antinuclear antibodies during the study, 3 subjects were negative at week 0 and showed positive inversion during the study. None of these positive inversion subjects exhibited the development of other autoimmune diseases.

Anti-Etanercept antibody

Seven (7) subjects with positive anti-etanercept antibody were found during week 24 through 96, however, no neutralizing antibody was found at any evaluation point.

1.3.3. Discussion on clinical aspects

A total of 32 paediatric subjects with polyarthritis type of active JRA, 8 from the study 204, 11 from the study 204 followed by the study 206-JA, and 13 from the study 208-JA, were enrolled and evaluated the safety of TNR-001 administered subcutaneously twice a week long term at doses of 0.2 mg/kg (up to 12.5 mg) or 0.4 mg/kg (up to 25 mg). All the 32 subjects were included in the efficacy and safety analyses.

Both 0.2 and 0.4 mg/kg groups well maintained the improvement observed after the previous studies in terms of the primary efficacy endpoints of JRA core set and other activity assessment measures. The results for the secondary endpoints (JRA30%DOI, JRA50%DOI, and JRA70%DOI, improvement rates of JRA core set and other activity assessment measures, drug characteristics and effect of subject characteristics, and evaluation of efficacy by Dose) and the other endpoints (cytokines and DAS28) also indicated that the improvement observed after the previous studies were well maintained. Despite small number of samples, the analyses by pattern of enrollment into the studies and pattern of dosing showed that all subjects who received the same dose of 0.4 mg/kg as the previous studies well maintained the improvements observed after the previous studies during this study, with the exception of 1 subject treated at 0.4 mg/kg in the studies 208-JA and 207-JA. On the other hand, 64.7% of subjects who received the same dose of 0.2 mg/kg as the previous studies showed no improvement in these endpoints but showed improvement after receiving an increased dose of 0.4 mg/kg, indicating that a dose of 0.2 mg/kg might be less efficacious in achieving disease control.

No deaths were reported throughout the study period. There were 7 SAEs in 6 subjects: Cataract in 2 subjects, campylobacter gastroenteritis and feeling abnormal cellulitis, back pain, and subcutaneous abscess in 1 subject for each. All the events were considered “not related” to the test article with the exception that cellulites, back pain, campylobacter gastroenteritis, and subcutaneous abscess were considered “possibly related” to the drug. As for outcomes, all the subjects were resolved with the exception in 1 subject (cataract: alleviated). Other than these events, however, the drug demonstrated good safety and tolerability.

Although it is difficult to reach a definite conclusion due to the limited number of subjects, this study suggested that the optimal dose of TNR-001 might be 0.4 mg/kg for treatment of JRA.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The results from Study 0881A1-207-JA are consistent with those already presented for the JIA indication in the Summary of Product Characteristics (SmPC). Therefore, as proposed by the MAH, no changes to the current SmPC are needed. The submission is satisfactory in terms of addressing the requirements of the MAH under Article 46 of Regulation (EC) No1901/2006, as amended.

Accordingly, this P46 procedure is considered fulfilled and no further regulatory action is considered necessary.

Recommendation

☒ **Fulfilled:**

No regulatory action required

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable