Report on the Deliberation Results

December 2, 2016

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand name	Ilaris for S.C. Injection 150 mg
Non-proprietary Name	Canakinumab (Genetical Recombination) (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	April 25, 2016

Results of Deliberation

In its meeting held on November 24, 2016, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the extremely limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct post-marketing surveillance on the safety and efficacy of the product covering all patients treated with the product throughout the re-examination period or until data of a specific number of patients are collected. The safety and efficacy of the product in long-term use, including the occurrence of infections, should be carefully evaluated based on the data collected.

**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ilaris for S.C. Injection 150 mg
Non-proprietary Name	Canakinumab (Genetical Recombination)
Applicant	Novartis Pharma K.K.
Date of Application	April 25, 2016
Dosage Form/Strength	Lyophilized injection in vials, each containing 180 mg of canakinumab (genetical recombination)[1)]
Application Classification	Prescription drug, (4) Drug with new indications, (6) Drug with new dosage
Items Warranting Special Mention	Orphan drug (Designation Nos.: No. 334 [*26 yaku*], No. 335 [*26 yaku*], and No. 336 [*26 yaku*], dated May 13, 2014, PFSB/ELD Notification No. 0513-1)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of familial Mediterranean fever refractory to conventional treatment, tumor necrosis factor receptor associated periodic syndrome, and hyperimmunoglobulin D syndrome (mevalonate kinase deficiency), and that the product has acceptable safety in view of its benefits.

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration as shown below, with the following conditions. Further investigation is necessary through post-marketing surveillance for the safety and efficacy of the Ilaris for S.C. Injection 150 mg in clinical use.

1) The vial is overfilled by 20% to compensate for loss during preparation to ensure that 1.0 mL of injectable solution containing 150 mg of canakinumab (genetical recombination) can be collected when reconstituted with 1.0 mL of JP water for injection.

Indications

1. The following cryopyrin-associated periodic syndromes

• Familial cold autoinflammatory syndrome

• Muckle-Wells syndrome

• Neonatal-onset multisystem inflammatory disease

2. Familial Mediterranean fever refractory to conventional treatment

3. Tumor necrosis factor receptor-associated periodic syndrome

4. Hyperimmunoglobulin D syndrome (mevalonate kinase deficiency)

(Underline denotes addition.)

Dosage and administration

Cryopyrin-associated periodic syndromes

The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 8 weeks.

Patients not achieving adequate clinical response (resolution of rash and other generalized inflammatory symptoms) may receive a gradually increased dose as needed. However, the maximum dose is 8 mg/kg for patients with a body weight of ≤40 kg and 600 mg for patients with a body weight of >40 kg.

If a disease flare occurs within 8 weeks of treatment at a maximum dose, the dose interval may be shortened to not less than 4 weeks.

The dose should be adjusted according to the patient's condition.

Familial Mediterranean fever and tumor necrosis factor receptor associated periodic syndrome

The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 4 weeks.

Patients not achieving adequate clinical response may receive an additional dose or gradually increased dose as needed. However, the maximum dose is 4 mg/kg for patients with a body weight of ≤40 kg and 300 mg for patients with a body weight of >40 kg.

Hyperimmunoglobulin D syndrome (mevalonate kinase deficiency)

The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 4 weeks.

Patients not achieving adequate clinical response may receive an additional dose or gradually increased dose as needed. However, the maximum dose is 6 mg/kg for patients with a body weight of ≤40 kg and 450 mg for patients with a body weight of >40 kg.

(Underline denotes addition.)

Conditions of approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the extremely limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct post-marketing surveillance on the safety and efficacy of the product covering all patients treated with the product throughout the re-examination period or until data of a specific number of patients are collected. The safety and efficacy of the product in long-term use, including the occurrence of infections, should be carefully evaluated based on the data collected.

Attachment

Review Report (1)

October 21, 2016

The following is an outline of the data submitted by the applicant and the content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Ilaris for S.C. Injection 150 mg
Non-proprietary Name	Canakinumab (Genetical Recombination)
Applicant	Novartis Pharma K.K.
Date of Application	April 25, 2016
Dosage Form/Strength	Lyophilized injection in vials, each containing 180.0 mg of canakinumab (genetical recombination)[2)]
Proposed Indications	Cryopyrin-associated periodic syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease) <u>Familial Mediterranean fever</u> <u>Tumor necrosis factor (TNF) receptor-associated periodic syndrome</u> <u>Mevalonate kinase deficiency/hyperimmunoglobulin D syndrome</u> (Underline denotes addition.)

Proposed Dosage and Administration

<u>Cryopyrin-associated periodic syndromes</u>

The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 8 weeks.

Patients not achieving adequate clinical response (resolution of rash and other generalized inflammatory symptoms) may receive a gradually increased dose as needed. However, the maximum dose is 8 mg/kg for patients with a body weight of ≤40 kg and 600 mg for patients with a body weight of >40 kg.

If a disease flare occurs within 8 weeks of treatment at a maximum dose, the

2) The vial is overfilled by 20% to compensate for loss during preparation to ensure that 1.0 mL of injectable solution containing 150 mg of canakinumab (genetical recombination) can be collected when reconstituted with 1.0 mL of JP water for injection.

dose interval may be shortened to not less than 4 weeks.

The dose should be adjusted according to the patient's condition.

Familial Mediterranean fever and tumor necrosis factor (TNF) receptor-associated periodic syndrome
The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 4 weeks.
If adequate clinical response has not been achieved, an additional dose of 2 mg/kg is administered to patients with a body weight of ≤40 kg and 150 mg to patients with a body weight of >40 kg as needed 7 days post-dose or later.
Also, as a general rule, the dose is increased to 4 mg/kg for patients with a body weight of ≤40 kg and 300 mg for patients with a body weight of >40 kg from the next dose 4 week later.

The dose should be adjusted according to the patient's condition. However, the maximum dose should not exceed 4 mg/kg for patients with a body weight of ≤40 kg and 300 mg for patients with a body weight of >40 kg.

Mevalonate kinase deficiency/hyperimmunoglobulin D syndrome
The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 4 weeks.

If adequate clinical response has not been achieved, an additional dose of 2 mg/kg is administered to patients with a body weight of ≤40 kg and 150 mg to patients with a body weight of >40 kg as needed 7 days post-dose or later.
Also, as a general rule, the dose is increased to 4 mg/kg for patients with a body weight of ≤40 kg, and 300 mg for patients with a body weight of >40 kg from the next dose 4 weeks later.

If the increased dose does not lead to adequate clinical response, an additional dose of 2 mg/kg is administered to patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg as needed 7 days post-dose or later. Also, as a general rule, the dose is increased to 6 mg/kg for patients with a body weight of ≤40 kg and 450 mg for patients with a body weight of >40 kg from the next dose 4 weeks later.

The dose should be adjusted according to the patient's condition. However, the maximum dose should not exceed 6 mg/kg for patients with a body weight of ≤40 kg and 450 mg for patients with a body weight of >40 kg.

(Underline denotes addition.)

Table of Contents

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information 4
2. Data Relating to Quality and Outline of the Rreview Conducted by PMDA..... 4
3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA 4
4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA..... 5
5. Toxicology and Outline of the Review Conducted by PMDA..... 5
6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA..... 5
7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA..... 9
8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA 32
9. Overall Evaluation during Preparation of Review Report (1)..... 32

List of Abbreviations

%CV	Coefficient of variation (in percent)
AUC_{last}	Area under the drug serum concentration-time curve (time 0 to the last measurable concentration sampling time)
AUC_{tau}	Area under the drug serum concentration-time curve during a dosing interval
C_{ave}	Average drug serum concentration
C_{max}	Maximal drug serum concentration
C_{min}	Minimal drug serum concentration
CAPS	Cryopyrin-associated periodic syndrome
CI	Confidence interval
crFMF	Colchicine resistant familial Mediterranean fever
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FMF	Familial Mediterranean fever
HIDS	Hyper IgD syndrome
HPF	Hereditary Periodic Fevers
IL	Interleukin
Ig	Immunoglobulin
MKD	Mevalonate kinase deficiency
PGA	Physician's global assessment of disease activity
SAA	Serum amyloid A
SJIA	Systemic juvenile idiopathic arthritis
TRAPS	TNF receptor-associated periodic syndrome

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Canakinumab (genetical recombination), the active ingredient of "Ilaris for S.C. Injection 150 mg," is a human IgG1 monoclonal antibody that blocks the activity of human IL-1β. Canakinumab was developed by Novartis. In Japan, Ilaris was approved for the indication of the treatment of cryopyrin-associated periodic syndromes (CAPS) in September 2011.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and familial Mediterranean fever (FMF) are autoinflammatory diseases classified as periodic fever syndromes, as with CAPS. As common characteristics of these diseases, patients present with recurrent systemic inflammations with high fever, which affect their normal daily activities, causing symptoms unique to the tissues and organs targeted by inflammatory cytokines. Colchicine is an approved drug for the treatment of FMF, but approximately 10% of the patients are either resistant or intolerant to colchicine. There is no established treatment for this patient population. Currently, there are no approved drugs for TRAPS and HIDS/MKD, and expectations for the development of a new drug are growing.

The clinical development of canakinumab for the treatment of TRAPS, HIDS/MKD, and FMF began in October 2010 outside Japan. Canakinumab was approved in the US in September 2016, and is under review in Europe as of October 2016.

In Japan, the clinical development of canakinumab for the treatment of TRAPS, HIDS/MKD, and FMF started in July 2014. Based on the results of studies including a multiregional clinical studies involving Japan, an application for partial change for canakinumab was filed to add TRAPS, HIDS/MKD, and FMF as indications and new dosage regimens for the additional indications.

Canakinumab was designated as an orphan drug with the expected indications of "mevalonate kinase deficiency," "tumor necrosis factor receptor associated periodic syndrome," and "familial Mediterranean fever" on May 13, 2014 (Designation Nos. 334 [*26 yaku*], 335 [*26 yaku*], and 336 [*26 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

No data on quality were submitted because the current application is intended for the new indications and new dosage regimens.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The current application is intended for the new indications and new dosage regimens, and because "non-clinical pharmacology study data" were already evaluated for the approval of the initial application, no new study results were submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The current application is intended for the new indications and new dosage regimens, and because "non-clinical pharmacokinetic study data" were already evaluated for the approval of the initial application, no new study results were submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

The current application is intended for the new indications and new dosage regimens, and no "toxicology data" were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The evaluation data submitted were the results of a foreign phase I study (CTD 5.3.1.2-1, Study A2104) in healthy adults. The concentrations of canakinumab in serum were measured by ELISA (lower limit of quantitation, 100 ng/mL), total IL-1β concentration in serum by sandwich ELISA (lower limit of quantitation, 0.5 pg/mL), and anti-canakinumab antibodies by electrochemiluminescence.

Unless otherwise noted, the dose level of Ilaris for S.C. Injection 150 mg is the dose level of canakinumab (genetical recombination).

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Bioequivalence study (CTD 5.3.1.2-1, Study A2104 [September 2010 to July 2011])

An open-label, randomized, parallel-group comparative study was conducted in 130 healthy adults outside Japan to study the bioequivalence of canakinumab between the lyophilized formulation (already approved in Japan) and the pre-filled syringe formulation (unapproved in Japan). Table 1 shows pharmacokinetic parameters following a single subcutaneous dose of the lyophilized or pre-filled syringe formulation 150 mg, indicating similar values between the formulations. The applicant explained that the composition of the pre-filled syringe formulation is identical to that of the liquid formulation in the vial (unapproved in Japan, used in a multiregional phase III study [Study N2301]) and that the equivalence/homogeneity in the quality of the lyophilized and vial liquid formulations was confirmed, and thus it is possible to file the partial change approval application for the lyophilized formulation with the clinical data package based on the multiregional phase III study (Study N2301) serving as the confirmatory study.

Table 1. Pharmacokinetic parameters of canakinumab following a single dose of the lyophilized or pre-filled syringe formulation

	Pre-filled syringe formulation (n = 66)	Lyophilized formulation (n = 63)	Geometric mean ratio of the formulations [90% CI] (Pre-filled syringe/lyophilized)
C_{max} (μg/mL)	19.66 ± 5.88	20.42 ± 6.66	0.99 [0.90, 1.08]
AUC_{last} (day·μg/mL)	705.81 ± 196.53	726.46 ± 174.33	1.01 [0.94, 1.09]
t_{max} (day)	4.96 (1.98, 14.00)	4.00 (2.00, 13.98)	
$t_{1/2}$ (day)	27.54 ± 6.68	27.40 ± 6.15	

Mean value ± standard deviation; t_{max}, are the median values (range)

6.2 Clinical pharmacology studies

6.2.1 Population pharmacokinetic analysis (CTD 5.3.3.5-1 and 5.3.3.5-3)

A population pharmacokinetic analysis was performed by NONMEM ver. 7.2 using serum concentration data of canakinumab (362 subjects, 3318 measurement points) from clinical studies (Studies N2301 [data of the double-blind period], D2203, D2304, D2306, and D2308) in patients with TRAPS, HIDS/MKD, or crFMF conducted in and outside Japan.

A 1-compartmental model with first-order elimination was used as the basic model. As the result of covariate selection,[3)] body weight was defined as the covariate for clearance and distribution volume. The final model was developed from a 1-compartmental model with first-order absorption and first-order elimination incorporating the selected covariate. Population parameters estimated by the final model (inter-individual variability [coefficient of variation, %CV]) were 0.14 L/day (30.8%) for clearance, and 4.96 L (27.2%) for volume of distribution. Another population pharmacokinetic analysis was performed by incorporating data for the withdrawal/treatment interval extension period of Study N2301, and the population parameters estimated by the final model (inter-individual variability [%CV]) were 0.14 L/day (30%) for clearance, and 5.02 L (27%) for volume of distribution.

Estimated pharmacokinetic parameters of C_{min}, $C_{ave,}$ and AUC_{tau} (median, [5th percentile, 95th percentile]) in patients with TRAPS, HIDS/MKD, and crFMF receiving canakinumab 150 mg every 4 weeks by subcutaneous injection were 16.4 [8.2, 30.7] μg/mL, 22.7 [12.2, 41.0] μg/mL, and 636.7 [341.6, 1147.2] μg·day/mL, respectively.

6.2.2 Exposure-response analysis (CTD 5.3.3.5-2 and 5.3.3.5-4)

An exposure-response analysis was performed using the efficacy and safety data from Study N2301 conducted in patients with TRAPS, HIDS/MKD, or crFMF, and serum canakinumab concentrations estimated by the population pharmacokinetic analysis model. Table 2 shows estimated serum canakinumab concentrations with or without flare. The results show that estimated serum canakinumab concentrations tend to be lower on visit days with flare than on visit days without flare.

3) Candidate covariates included the effects of body weight on clearance, age, sex, baseline albumin concentration, baseline diseases, and the effects of body weight on the volume of distribution.

A logistic regression model was established with the presence or absence of flare[4)] defined as the outcome variable and E_{max} function of the estimated serum canakinumab concentrations as the explanatory variable, and the relationship between the probability of flare and estimated serum canakinumab concentrations was modeled based on the logistic regression model. Figure 1 shows the relationship between the probability of flare occurrence and estimated serum canakinumab concentrations calculated by the developed exposure-response model. The concentration that would cause 50% reduction of the logit of the probability of flare (= probability of flare / [1 − logarithm of the probability of flare]) was estimated as 10.35 µg/mL in patients with TRAPS or HIDS/MKD, and 1.60 µg/mL in patients with crFMF.

Table 2. Estimated serum canakinumab concentrations in the presence and absence of flare

	Concentration on the visit day when a flare was observed	Concentration on the visit day when a flare was not observed
TRAPS	8.2 [6.2, 10.8] µg/mL	12.2 [10.5, 14.3] µg/mL
MKD/HIDS	8.9 [7.4, 10.6] µg/mL	11.9 [10.5, 13.4] µg/mL
crFMF	4.3 [3.2, 5.8] µg/mL	9.8 [8.6, 11.2] µg/mL

Geometric mean [95% CI]

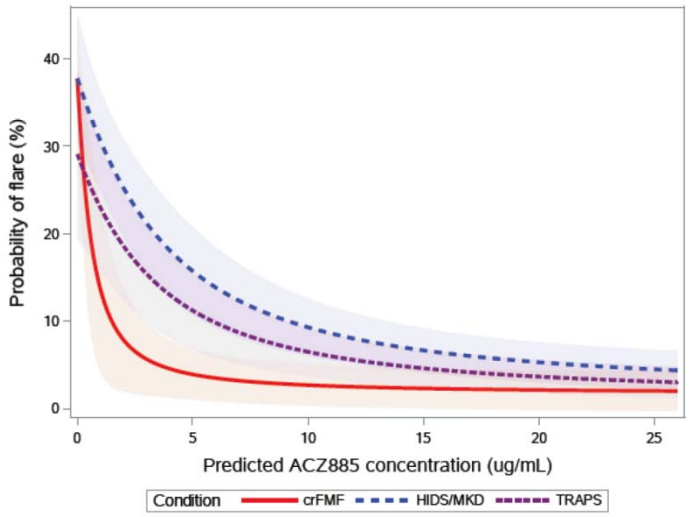

Figure 1. The relationship between the probability of flare and estimated serum canakinumab concentration

The safety data was used to investigate the relationship between abnormal hematological parameters of canakinumab used for the previously approved indication (CTC Grade ≥1 neutrophil count decreased, lymphocyte count decreased to below the lower limit of normal, CTC Grade ≥1 white blood cell count decreased, and CTC Grade ≥1 platelet count decreased) and the estimated serum canakinumab concentrations. No concentration-dependent increase was observed in the risk of these abnormalities.

4) A flare was defined in Study N2301 as a PGA score of 2 (mild) or higher, and CRP ≥30 mg/L.

6.R Outline of the review conducted by PMDA

6.R.1 Starting dose levels and administration of canakinumab from a clinical pharmacological viewpoint

The applicant's rationale for the starting dosage regimen of canakinumab for patients with TRAPS, HIDS/MKD, or crFMF, specifically, 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg to be administered every 4 weeks:

Due to the extremely small number of Japanese and non-Japanese patients with TRAPS, HIDS/MKD, or FMF, a dose-finding study seemed unfeasible. The dosage regimen used in studies (Studies D2203, D2204, and DTR01) in patients with TRAPS or crFMF conducted overseas to explore the efficacy of canakinumab was 150 mg (or 2 mg/kg for subjects weighing ≤40 kg) every 4 weeks by subcutaneous injection. The regimen was determined based on the investigators' knowledge from experience, i.e., the treatment of TRAPS, HIDS/MKD, or FMF requires a higher dose of anakinra,[5)] an interleukin-1 receptor antagonist, than the treatment of CAPS.

A relationship between the serum concentration of canakinumab and flare in patients with TRAPS, HIDS/MKD, or crFMF was investigated based on the results from Study N2301 using the logistic regression model [see Section 6.3]. Steady-state C_{min} values in patients weighing ≤40 kg receiving 2 mg/kg of canakinumab and in those weighing >40 kg receiving 150 mg, both at 4-week intervals, were estimated to be greater than the concentration that decreases the logit of the probability of flare by 50% in approximately 76% of the patients with TRAPS or HIDS/MKD and in approximately 100% of the patients with crFMF. Based on the estimation, a certain level of flare suppression is expected at the proposed dosage regimen. Furthermore, the C_{min} of canakinumab 16 weeks after the start of treatment every 4 weeks at 2 mg/kg in patients weighing ≤40 kg and at 150 mg in patients weighing >40 kg was estimated based on the population pharmacokinetic analysis. The C_{min} of canakinumab (median value, with maximum and minimum values in the brackets) was 10.1 [2.7, 39.2] μg/mL, and 15.5 [3.0, 57.1] μg/mL in patients weighing ≤40 kg and those weighing >40 kg, respectively, suggesting that the exposure was slightly higher in patients weighing >40 kg than in patients weighing ≤40 kg. In Study N2301, efficacy and safety were assessed by body weight. As shown in Table 3, the results of some parameters differ by body weight class or dose level. At the same time, there is large inter-subject variability with no constant trend of decreasing efficacy in the subgroup of patients weighing ≤40 kg. Therefore, it was considered unlikely that the difference in exposure due to different body weight would affect the efficacy or safety of canakinumab.

5) In other countries, anakinra has been approved for indications including CAPS and rheumatoid arthritis; however, it has not been approved for the indications of TRAPS, HIDS/MKD, or FMF.

Based on the above, it is considered possible to set the dosage regimen of canakinumab for suppression of flares as: administration every 4 weeks at 2 mg/kg for patients with a body weight of ≤40 kg, and 150 mg for patients with a body weight of >40 kg.

Table 3. Efficacy and safety of canakinumab by body weight in Study N2301 (Week 16; subjects randomized to the canakinumab group)

Efficacy and safety endpoints	Patients with TRAPS		Patients with HIDS/MKD		Patients with crFMF	
	Body weight ≤40 kg	Body weight >40 kg	Body weight ≤40 kg	Body weight >40 kg	Body weight ≤40 kg	Body weight >40 kg
Starting dose	2 mg/kg	150 mg	2 mg/kg	150 mg	2 mg/kg	150 mg
Percentage of subjects with remission[a)] after 16 weeks of treatment	27 (3/11)	64 (7/11)	28 (5/18)	42 (8/19)	78 (7/9)	5 (12/22)
CRP (mg/L)[b)]	9.6 ± 14.6	9.8 ± 14.2	27.9 ± 36.8	10.5 ± 14.7	4.0 ± 3.0	5.4 ± 3.8
SAA (mg/L)[b)]	265.2 ± 755.7	24.6 ± 24.8	1420 ± 3176	184.8 ± 434.4	59.4 ± 123.0	32.1 ± 34.0
PGA is <2[a)]	73 (8/11)	91 (10/11)	88 (15/17)	95 (18/19)	100 (9/9)	91 (20/22)
Total IL-1β concentration in serum (ng/L)[b)]	37.8 ± 25.4	14.2 ± 5.0	55.6 ± 50.8	34.9 ± 28.9	39.3 ± 20.8	33.2 ± 17.3
Absolute neutrophil count ($\times 10^9$/L)[b)]	2.7 ± 1.3	3.2 ± 1.3	3.4 ± 1.7	3.3 ± 1.4	3.4 ± 2.0	3.0 ± 1.3
Lymphocyte count low[a)]	0 (0/11)	0 (0/11)	0 (0/18)	5 (1/19)	0 (0/9)	9 (2/22)
Neutrophil count low[a)]	9 (1/11)	9 (1/11)	11 (2/18)	5 (1/19)	11 (1/9)	9 (2/22)
Platelet count low[a)]	0 (0/11)	0 (0/11)	11 (2/18)	21 (4/19)	22 (2/9)	18 (4/22)
White blood cell count low[a)]	0 (0/11)	9 (1/11)	16 (3/18)	16 (3/19)	0 (0/9)	5 (1/22)

Notes: a) % (number of subjects); b) mean ± standard deviation

PMDA's view:

Based on the explanation of the applicant, it is understandable that the starting dose was specified as 150 mg (or 2 mg/kg for patients with a body weight of ≤40 kg) administered every 4 weeks from a clinical pharmacological viewpoint. The validity of the proposed dosage and administration including dose increase will be determined based on the efficacy and safety results and other factors [see Section "7.R.4 Dosage and administration"].

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The efficacy and safety evaluation data submitted were the results of a multiregional phase III study (CTD 5.3.5.1-1, Study N2301) in patients with TRAPS, HIDS/MKD, or crFMF.

7.1 Phase III study

7.1.1 Multiregional phase III study in patients with TRAPS, HIDS/MKD, or crFMF (5.3.5.1-1, Study N2301 [Ongoing since June 2014, data cut-off in February 2016])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in patients with TRAPS,[6] HIDS/MKD,[7] or crFMF[8] (target number of subjects, 180 [60 in each cohort; 30 in each group]) in 16 countries including Japan, Italy, Spain, and Turkey to evaluate the efficacy and safety of canakinumab.

This study consisted of 3 periods (the double-blind period ending before Week 17, the withdrawal/treatment interval extension period starting at Week 17 and ending before Week 41, and the open-label period starting at Week 41 and ending before Week 113) (Figure 2). In the double-blind period, patients received canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) or placebo by subcutaneous injection every 4 weeks. If persistent disease activity or flare was observed on Days 8 to 28, patients received only 1 additional dose of canakinumab 150 mg (or 2 mg/kg) under blinded condition in accordance with the criteria in Table 4, followed by canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) every 4 weeks in the canakinumab group and canakinumab 150 mg (or 2 mg/kg) every 4 weeks in the placebo group under blinded condition at subsequent scheduled visits. On Day 29 onward, if disease remained mild, moderate, or severe according to physician's global assessment with CRP of≥30 mg/L, patients in the canakinumab group received canakinumab 300 mg (or 4 mg/kg) and those in the placebo group received canakinumab 150 mg (or 2 mg/kg) every 4 weeks in an unblinded manner. For patients not responding even to the modified dose, the dose could be further increased up to 300 mg every 4 weeks. During the withdrawal/treatment interval extension period, subjects received canakinumab or placebo by subcutaneous injection as shown in Figure 2. In the open-label period, subjects continued receiving canakinumab under the same regimen as that at the end of the withdrawal/treatment interval extension period.

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6) Patients who were found to have (a) a diagnosis of TRAPS without active flare, (b) *TNFRSF1A* gene mutation, and (c) periodic repetitive disease activity at screening, and (d) a mild, moderate, or severe clinical flare of TRAPS according to physician's global assessment and (e) CRP of >10 mg/L at randomization.

7) Patients who were found to have (a) a diagnosis of HIDS without active flare, (b) a genetic or enzymatic diagnosis of HIDS, and (c) ≥3 episodes of febrile flares of HIDS in the past 6 months at screening, and (d) a mild, moderate, or severe clinical flare of HIDS according to a physician's global assessment, and (e) CRP of >10 mg/L at randomization.

8) Patients who were found to have (a) a diagnosis of Type 1 FMF according to Tel-Hashomer criteria without active flare, (b) ≥1 known mutations in exon 10 of the *MEFV* gene, (c) active disease despite colchicine therapy (1.5-3.0 mg/day or a dose and dosage regimen adjusted for the age/body weight of pediatric patients), or intolerance to an effective dose of colchicine, (d) ≥1 episode of flare per month at screening, and (e) acute flares of crFMF persisting for 12 to 72 hours, (f) a mild, moderate, or severe clinical flare of crFMF according to a physician's global assessment, and (g) CRP of >10 mg/L at randomization.

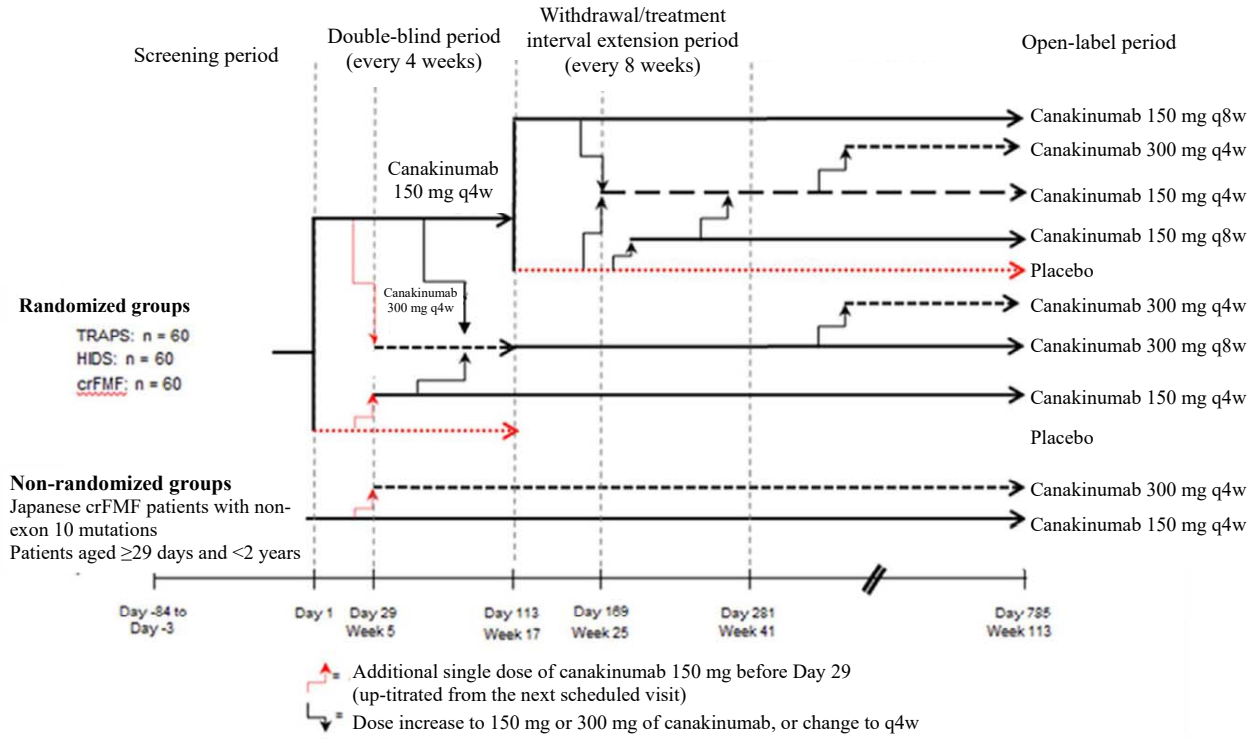

Figure 2. Assignment of subjects and treatment plan in Study N2301

Table 4. Criteria for dose addition or increase in the double-blind period (Study N2301)

	Criteria for dose addition or increase			Administration of an additional dose of the study drug	Dose increase at the scheduled visit
	Physician's global assessment		CRP		
Days 8-14	Mild, moderate, or severe	OR	>10 mg/L and decrease by <40% from baseline	Acceptable	Blinded dose increase at the next scheduled visit (Day 29)
Day 15	Mild, moderate, or severe	OR	>10 mg/L and decrease by <70% from baseline	Acceptable[a)]	Blinded dose increase at the next scheduled visit (Day 29)
Days 16-28	Mild, moderate, or severe	OR	>10 mg/L and decrease by <70% from baseline	Acceptable[a)]	Blinded dose increase at the next scheduled visit (Day 29)
Days 29-112	Mild, moderate, or severe	AND	≥30 mg/L		Open-label dose increase at the next scheduled visit (including Day 29)

a) If the patient had not received any additional dose

A total of 181 subjects (46 subjects with TRAPS [22 in the canakinumab group and 24 in the placebo group], 72 subjects with HIDS/MKD [37 in the canakinumab group and 35 in the placebo group], and 63 subjects with crFMF [31 in the canakinumab group and 32 in the placebo group]) were randomized. All were included in the FAS and in the safety analysis population. The FAS was used for the efficacy analysis. The safety analysis population included non-randomized patients, i.e., 2 Japanese patients with crFMF presenting non-exon 10 mutations of the *MEFV* gene who received canakinumab 150 mg every 4 weeks by subcutaneous injection and 2 patients with HIDS/MKD aged ≥29 days and <2 years. In the double-blind period, treatment discontinuation occurred in 2 subjects with TRAPS in the placebo group (lack of efficacy, and consent withdrawal in 1 subject each); 3 subjects with HIDS/MKD, 1 in the canakinumab group (adverse event) and 2 in the placebo group (adverse event and lack of efficacy in 1

subject each); and 1 subject with crFMF in the placebo group (consent withdrawal). Treatment discontinuation also occurred in 1 non-randomized patient with HIDS/MKD aged <2 years (adverse event).

The FAS Japanese subgroup consisted of 8 subjects (6 subjects with TRAPS [2 in the canakinumab group and 4 in the placebo group], 1 subject with HIDS/MKD [placebo group] and 1 subject with crFMF [placebo group]). No treatment discontinuation occurred in the Japanese subgroup.

Table 5 shows the remission rates (the proportion of subjects whose index flare[9)] by Day 15 and did not experience a new flare[10)] during the 16-week treatment period[11)]), which is the primary efficacy endpoint. In the primary analysis, there were statistically significant differences between the placebo and canakinumab groups for all primary diseases, demonstrating the superiority of canakinumab over placebo.

Table 5. Remission rates after 16 weeks from the start of treatment (FAS)

	Canakinumab	Placebo	Difference from placebo group [95% CI][a)] and *P*-value[b)]
TRAPS	45 (10/22)	8 (2/24)	37 [8, 61] *P* = 0.0050
HIDS/MKD	35 (13/37)	6 (2/35)	29 [6, 50] *P* = 0.0020
crFMF	61 (19/31)	6 (2/32)	55 [31, 73] *P* < 0.0001

% (number of subjects)
[a)] Exact confidence interval
[b)] Fisher's exact test

Table 6 shows the results in the Japanese subgroup. On Days 8 to 28, 6 subjects initially randomized to the placebo group experienced a flare, and they were treated with blinded canakinumab.

9) The initial flare at randomization was defined as the index flare. The flare was considered to have resolved when (a) it was assessed as minimal or no disease by physician's global assessment and (b) CRP was ≤10 mg/L or decreased by ≥70% from baseline.

10) A clinical flare (assessed as mild, moderate, or severe by physician's global assessment) and a serological flare (CRP ≥30 mg/L) occurred at a time.

11) Subjects in the canakinumab group receiving the increased dose and subjects in the placebo group shifted to canakinumab, and those withdrawn from the study by Week 16 were considered to have failed to achieve remission. Subjects who had received an additional dose of blinded canakinumab by Day 15 were considered to have failed to achieve remission of the index flare on Day 15.

Table 6. Physician's global assessment and inflammation markers up to Week 16 (Japanese subgroup)

Disease type	Treatment group	Additional dose/dose increase	Evaluation time point	Physician's global assessment[12)]	CRP (mg/L)	SAA (mg/L)
TRAPS	Canakinumab	None	Baseline	Mild	192.50	8977
			Day 13	No disease	1.50	5
			Day 29	No disease	0.50	6
			Week 17	No disease	2.00	26
	Canakinumab	An additional dose of canakinumab administered on Day 8, Canakinumab 300 mg from Day 29	Baseline	Moderate	855.00	> 600
			Day 15	No disease	65.00	8
			Day 29	No disease	0.00	4
			Week 17	No disease	0.00	< 4
	Placebo	An additional dose of canakinumab administered on Day 10, Canakinumab 150 mg from Day 22	Baseline	Mild	73.50	97
			Day 10	Mild	5.50	4
			Day 22	Mild	2.00	6
			Week 17	Mild	2.00	< 4
	Placebo	An additional dose of canakinumab administered on Day 15, Canakinumab 150 mg from Day 29	Baseline	Mild	14.00	< 4
			Day 15	Mild	18.50	< 4
			Day 29	Mild	2.00	< 4
			Week 17	Mild	1.50	< 4
	Placebo	An additional dose of canakinumab administered on Day 13, Canakinumab 150 mg from Day 29	Baseline	Mild	380.50	> 12000
			Day 13	Mild	500.00	> 12000
			Day 29	No disease	13.50	26
			Week 17	No disease	22.50	89
	Placebo	An additional dose of canakinumab administered on Day 15; Canakinumab 150 mg from Day 29	Baseline	Mild	14.00	10
			Day 15	Mild	9.00	13
			Day 29	Minimal	28.00	32
			Week 17	No disease	1.00	< 4
HIDS/ MKD	Placebo	An additional dose of canakinumab administered on Day 8; Canakinumab150 mg from Day 33	Baseline	Mild	385.00	> 600
			Day 17	No disease	5.00	7
			Day 33	No disease	40.00	92
			Week 17	No disease	5.00	10
crFMF	Placebo	An additional dose of canakinumab administered on Day 15; Canakinumab150 mg from Day 29	Baseline	Mild	20.00	6
			Day 15	Moderate	160.00	144
			Day 29	No disease	3.00	< 4
			Week 17	No disease	2.00	< 4

During the double-blind period, the number of subjects who experienced adverse events were 33 of 43 subjects with TRAPS (77%) receiving canakinumab or those who were shifted to canakinumab, 3 of 3 subjects with TRAPS (100%) continuing with placebo, 59 of 68 subjects with HIDS/MKD (87%) receiving canakinumab, and 4 of 4 HIDS/MKD subjects (100%) continuing with placebo. Adverse events occurred also in subjects with crFMF, specifically, 47 of 58 (81%) receiving canakinumab and 4 of 5 (80%) continuing with placebo. Table 7, 8, and 9 show major adverse events. No deaths occurred.

12) Before the CRP results were obtained, global assessment of disease activity was performed by the investigator using the 5-stage rating system (no disease, minimal, mild, moderate, and severe).

Table 7. Adverse events observed in ≥5% of subjects who received canakinumab (TRAPS, safety analysis population, double-blind period)

Adverse event	Subjects who received canakinumab (n = 43)	Subjects who continued to receive placebo (n = 3)
Pyrexia	6 (14)	0
Abdominal pain	5 (12)	0
Injection site reaction	5 (12)	0
Nasopharyngitis	5 (12)	0
Abdominal pain upper	4 (9)	0
Rhinitis	4 (9)	0
Upper respiratory tract infection	4 (9)	0
Vomiting	4 (9)	0
Cough	3 (7)	0
Headache	3 (7)	1 (33)
Rash	3 (7)	0
Tumour necrosis factor receptor-associated periodic syndrome	3 (7)	0

Number of subjects (%)

Table 8. Adverse events observed in ≥5% of subjects who received canakinumab (HIDS/MKD, safety analysis population, double-blind period)

Adverse event	Subjects who received canakinumab (n = 68)	Subjects who continued to receive placebo (n = 4)
Pyrexia	16 (24)	1 (25)
Headache	12 (18)	0
Diarrhoea	8 (12)	0
Oropharyngeal pain	8 (12)	0
Abdominal pain	7 (10)	2 (50)
Arthralgia	7 (10)	0
Cough	7 (10)	0
Nasopharyngitis	7 (10)	1 (25)
Upper respiratory tract infection	6 (9)	0
Gastroenteritis	5 (7)	0
Hyper IgD syndrome	5 (7)	0
Injection site reaction	5 (7)	0
Lymphadenopathy	5 (7)	0
Rhinitis	5 (7)	0
Abdominal pain upper	4 (6)	0
Respiratory tract infection	4 (6)	0

Number of subjects (%)

Table 9. Adverse events observed in ≥5% of subjects who received canakinumab (crFMF, safety analysis population, double-blind period)

Adverse event	Subjects who received canakinumab (n = 58)	Subjects who continued to receive placebo (n = 5)
Familial Mediterranean fever	13 (22)	2 (40)
Injection site reaction	8 (14)	0
Diarrhoea	7 (12)	0
Abdominal pain	6 (10)	1 (20)
Headache	6 (10)	1 (20)
Nasopharyngitis	6 (10)	0
Upper respiratory tract infection	5 (9)	0
Influenza like illness	4 (7)	1 (20)
Erythema	3 (5)	0
Pyrexia	3 (5)	1(20)
Tonsillitis	3 (5)	0

Number of subjects (%)

Serious adverse events occurred in 2 subjects with TRAPS who received canakinumab (dysphagia/laryngeal stenosis/oropharyngeal pain/vomiting [1] and tumour necrosis factor receptor-associated periodic syndrome [1]), 8 subjects with HIDS/MKD who received canakinumab (pneumonia [2], suicide attempt/self injurious behaviour [1], mevalonate kinase deficiency [1], polyserositis/pericarditis [1], seizure [1], and familial Mediterranean fever/hyper IgD syndrome/pharyngitis/conjunctivitis [1], and abdominal pain [1]), 2 subjects with HIDS/MKD who received placebo (diarrhoea infectious [1], and neutropenia [1]), 5 subjects with crFMF who received canakinumab (bile duct stone/hepatic cirrhosis/ascites/granulomatous liver disease [1], umbilical hernia [1], familial Mediterranean fever [1], pharyngotonsillitis [1], and obesity [1]) and 1 subject with crFMF who continued to receive placebo (cough/atypical pneumonia). A causal relationship to the study drug could not be ruled out for the event in 1 subject with HIDS/MKD who continued to receive placebo (neutropenia), 2 subjects with crFMF who received canakinumab (granulomatous liver disease [1], and pharyngotonsillitis [1]), and 1 subject with crFMF who received placebo (atypical pneumonia).

Adverse events led to treatment discontinuation in 2 subjects with HIDS/MKD who received canakinumab (pericarditis [1], and hyper IgD syndrome [1]), and 1 subject with HIDS/MKD who continued to receive placebo (neutropenia). A causal relationship to the study drug could not be ruled out for neutropenia in the subject who continued to receive placebo. There were no adverse events leading to treatment discontinuation in subjects with TRAPS or crFMF.

Adverse drug reactions occurred in 14 subjects with TRAPS who received canakinumab, and 1 subject with TRAPS who continued to receive placebo; 21 subjects with HIDS/MKD who received canakinumab, and 1 subject with HIDS/MKD who continued to receive placebo and 19 subjects with crFMF who received canakinumab, and 1 subject with crFMF who continued to receive placebo.

Adverse events occurred in all 4 non-randomized subjects. No deaths occurred. Serious adverse events occurred in 1 subject with HIDS/MKD (hepatic failure/pancytopenia), and this subject also experienced adverse events leading to treatment discontinuation (hepatic failure/pancytopenia/hypophosphataemia/hypocalcaemia). A causal relationship to the study drug could not be ruled out for the serious adverse events in this subject. Hepatic failure resolved by Week 36 and pancytopenia by Week 16.

Adverse events occurred in all 8 subjects in the Japanese subgroup. Adverse events that occurred in ≥2 subjects were nasopharyngitis [2], oropharyngeal pain [2], and urticaria [2]. There were no adverse events resulting in deaths, serious adverse events, or adverse events leading to treatment discontinuation. Adverse drug reactions occurred in 4 subjects.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Design of the phase III study

The applicant's explanation about the design of Study N2301 in patients with TRAPS, HIDS/MKD, and crFMF:

Implementation of a multiregional study

TRAPS, HIDS/MKD, and FMF are extremely rare diseases. Because of the low feasibility of ≥1 clinical study or a confirmatory study in 1 single region, a multiregional phase III study was designed to develop a clinical data package. The enrollment of Japanese patients in the multiregional phase III study was planned for the following reasons:

- There were no significant differences in the diagnostic or treatment systems for TRAPS, HIDS/MKD, and FMF between Japan and other countries.
- There were no obvious pharmacokinetic or pharmacodynamic differences between Japanese and non-Japanese subjects when canakinumab was administered to healthy subjects and patients with CAPS (see Review Report for Ilaris for S.C. Injection 150 mg, dated on August 9, 2011).

Approximately 40% of Japanese patients with FMF have non-exon 10 mutations. Therefore, Study N2301 was designed to enroll Japanese FMF patients with non-exon 10 mutations of the *MEFV* gene. Japanese FMF patients with non-exon 10 mutations of the gene were included in the non-randomized group because the effect of the difference in mutation site on the efficacy of canakinumab was not known.

Primary endpoint and secondary endpoints

Because periodic fever syndromes are rare diseases that were identified only recently, indicators for efficacy evaluation have not been established. Accordingly, the primary endpoint of Study N2301 was the proportion of patients experiencing remission, a combined index of physician's global assessment

of disease activity (PGA) and CRP as the inflammatory marker. The endpoint was aimed to evaluate clinically significant decrease in disease activity as with the clinical studies in patients with CAPS conducted in Japan and overseas.

Because the majority of patients show high levels of nonspecific inflammation markers during a disease flare, the following parameters were selected as secondary endpoints: clinical remission (physician's global assessment of minimal or no disease), serological remission (normalized CRP, ≤10 mg/L), and normalized serum amyloid A (SAA) (≤10 mg/L).

Rationale for the dosage and administration

Studies D2203, D2402, D2204, and DTR01 were conducted overseas Japan to explore the efficacy of canakinumab in patients with TRAPS, HIDS/MKD, or crFMF. The study investigators knew from experience that the dose of anakinra,[5)] an interleukin-1 receptor antagonist, must be higher when used for the treatment of TRAPS, HIDS/MKD, or FMF than that for the treatment of CAPS. Accordingly, these studies used the following dosage regimes that were higher than required for CAPS.

- Studies D2203, D2204, and DTR01 in patients with TRAPS or crFMF:

Subcutaneous canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) every 4 weeks
For patients with inadequate response, subcutaneous canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) every 4 weeks

- Study D2402 in patients with HIDS/MKD:

Subcutaneous canakinumab 300 mg (or 4 mg/kg for patients weighing ≤40 kg) every 6 weeks
For patients with inadequate response, subcutaneous canakinumab 450 mg (or 6 mg/kg for patients weighing ≤40 kg) every 6 weeks

The results of these foreign studies suggested improvement in clinical symptoms and inflammation markers, and reduction in the number of flares. Therefore, Study N2301 used the starting dose of 150 mg every 4 weeks for all 3 primary diseases, which was to be increased to 300 mg as necessary, to accommodate different disease activities.

PMDA's view:

Given the extremely small number of Japanese patients with the diseases, for the clinical development of canakinumab to treat TRAPS, HIDS/MKD, or FMF, the applicant planned to enroll Japanese patients to the multiregional phase III study without conducting a dose-finding study. The dosage regimen of canakinumab was determined, based on the results from foreign clinical studies, as the starting dose of 150 mg every 4 weeks for all 3 diseases that was to be increased to 300 mg for patients with inadequate response. These applicant's decisions are acceptable. Prolonged frequent attacks and inflammation is suggested to result in amyloidosis, which may affect the vital prognosis (*Nat Rev Rheumatol.*

2009;5:249-56, *Ann Rheum Dis.* 2016;75:644-51). The primary endpoint allows the evaluation of both PGA and the inflammation marker, and selecting such primary endpoint is clinically significant. Because of as few as 8 Japanese subjects randomized to the canakinumab or placebo group and 3 in the non-randomized group, Study N2301 evaluated efficacy in Japanese subjects on an individual basis.

7.R.1.2 Efficacy at the starting dose and dosage regimen

The applicant's explanation about the efficacy of canakinumab at the starting dosage regimen:

The superiority of canakinumab 150 mg over placebo was demonstrated in the primary efficacy endpoint, i.e., the proportion of patients with TRAPS, HIDS/MKD, or crFMF experiencing remission after 16-week treatment, [see Section "7.1 Phase III study"]. Table 10 shows the results of the secondary endpoints, namely, the proportions of subjects who achieved clinical remission (minimal or no disease by physician's global assessment), serological remission (CRP of ≤10 mg/L), and normalized SAA (≤10 mg/L) after 16-week treatment. The results indicate the superior efficacy of canakinumab 150 mg over placebo for all 3 diseases, as indicated by the results of the primary endpoint.

Table 10. Proportions of subjects experiencing clinical remission, serological remission, or normalized SAA after 16-week treatment (FAS)

	TRAPS			HIDS/MKD			crFMF		
	Canakinumab	Placebo	Risk difference [95% CI]	Canakinumab	Placebo	Risk difference [95% CI]	Canakinumab	Placebo	Risk difference [95% CI]
Clinical remission	45 (10/22)	4 (1/24)	41 [13, 65]	46 (17/37)	6 (2/35)	40 [18, 60]	65 (20/31)	9 (3/32)	55 [31, 73]
Serological remission	37 (8/22)	8 (2/24)	28 [−1, 54]	41 (15/37)	6 (2/35)	35 [12, 55]	68 (21/31)	6 (2/32)	61 [38, 78]
Normalization of SAA	27 (6/22)	0 (0/24)	27 [−1, 54]	14 (5/37)	3 (1/35)	11 [−13, 33]	26 (8/31)	0 (0/32)	26 [1, 48]

Upper row, %; lower row, number of subjects

Furthermore, subgroup analyses were performed on the primary endpoint of Study N2301 by age (<18 years vs. ≥18 years), prior treatment with a biological agent, concomitant use of colchicine. The results showed no significant difference between subgroups (Table 11).

Table 11. Subgroup analysis results on the proportion of subjects experiencing remission after 16-week treatment (FAS)

		TRAPS		HIDS/MKD		crFMF	
		Canakinumab	Placebo	Canakinumab	Placebo	Canakinumab	Placebo
Age	≥18 years	63 (5/8)	9 (1/11)	44 (4/9)	0	53 (9/17)	6 (1/17)
	<18 years	36 (5/14)	8 (1/13)	32 (9/28)	8 (2/26)	71 (10/14)	7 (1/15)
Biological agent	With prior treatment	50 (4/8)	13 (1/8)	11 (1/9)	0	57 (4/7)	0
	No prior treatment	43 (6/14)	6 (1/16)	43 (12/28)	6 (2/31)	63 (15/24)	8 (2/24)
Concomitant colchicine	Used					62 (18/29)	0
	Not used					50 (1/2)	33 (2/6)

% (number of subjects)

Table 6 shows the results of Japanese subjects in the double-blind period. Index flare did not resolve in all 6 subjects initially randomized to the placebo group, who therefore received canakinumab by Day 15. Following the treatment with canakinumab 150 mg every 4 weeks or the increased dose of 300 mg, all these Japanese subjects achieved "minimal" or "no disease" by the physician's global assessment with improved inflammation marker levels.

The 3 subjects in the non-randomized group were Japanese patients (Table 12). The 2 patients with crFMF presenting with non-exon 10 mutations of the *MEFV* gene achieved remission, and another 1 patient with HIDS/MKD aged <2 years experienced index flare resolution by Day 15. However, the study was discontinued on Day 45 due to adverse events (hepatic failure, hypocalcaemia, hypophosphataemia, and pancytopenia) [see Section "7.R.2.3 Liver disorder"].

Table 12. Physician's global assessment and inflammation markers by Week 16 (non-randomized group, Japanese subjects)

Disease type/treatment group	Dosage regimen	Time assessed	Physician's global assessment[13)]	CRP (mg/L)	SAA (mg/L)
HIDS/MKD (<2 years) Non-randomized group	150 mg every 4 weeks (no dose increase)	Baseline	Moderate	117.00	823
		Day 16	Minimal	19.00	153
		Day 30	Minimal	25.00	242
		Day 45[a)]	Minimal	21.00	61
crFMF (Non-exon 10 mutations) Non-randomized group	150 mg every 4 weeks (no dose increase)	Baseline	Mild	159.00	5195
		Day 17	Minimal	0.50	6
		Day 38	Minimal	0.50	< 4
		Week 17	Minimal	0.50	4
crFMF (Non-exon 10 mutations) Non-randomized group	150 mg every 4 weeks (no dose increase)	Baseline	Moderate	45.00	290
		Day 19	Minimal	0.00	< 4
		Day 28	Minimal	0.00	< 4
		Week 17	Minimal	0.00	< 4

[a)] Final assessment point (study was discontinued on Day 45)

PMDA's view:

In Study N2301, the superiority of canakinumab over placebo was demonstrated in the primary efficacy endpoint, i.e., the proportion of subjects with remission after 16-week treatment of TRAPS, HIDS/MKD, and crFMF. Similar trends were observed in the results of the secondary endpoints, i.e., the proportions of subjects who achieved clinical remission, serological remission, and normalized SAA.

[13)] Before the CRP results were obtained, global assessment of disease activity was performed by the investigator, using the 5-stage rating system (absent, minimal, mild, moderate, and severe).

Therefore, it was concluded that the efficacy of canakinumab was demonstrated in the treatment of these diseases. In Japanese subjects, albeit few in number, the symptoms and the levels of the inflammation markers improved. Treatment with canakinumab at the starting dose of 150 mg every 4 weeks is therefore expected to be effective in Japanese patients with TRAPS, HIDS/MKD, or crFMF.

7.R.1.3 Efficacy after dose increase

The applicant's explanation about the efficacy of canakinumab after dose increase:

The proportion of subjects experiencing remission after 16-week canakinumab treatment at the starting dose (150 mg every 4 weeks) were: 45% (10 of 22) of subjects with TRAPS, 35% (13 of 37) of subjects with HIDS/MKD, and 61% (19 of 31) of subjects with crFMF. The results suggest that symptoms were not able to be controlled at 150 mg of canakinumab in approximately half of the subjects. In the treatment of periodic fever syndromes, one of the critical treatment objectives is to minimize the frequency of attacks to suppress the progression of amyloidosis. Therefore, the efficacy of increased doses of canakinumab was evaluated by comparing the results of an exploratory analysis on the proportion of subjects experiencing remission (the proportion of subjects experiencing remission, including subjects who had achieved remission defined in the primary analysis and subjects in the canakinumab group who received an additional dose of 150 mg or increased dose of 300 mg from Days 8 to 28 and achieved index flare resolution by Day 29 without having a new flare after that) with the primary analysis results. Further, the proportion of subjects in the canakinumab group who received an additional dose of 150 mg or increased dose of 300 mg from Days 8 to 28 and achieved index flare resolution not by Day 15 but by Day 29 was calculated to evaluate the efficacy of additional doses of canakinumab.

Table 13 shows a breakdown of the subjects who were initially randomized to the canakinumab group and received an increased dose of 300 mg during the double-blind period and subjects who further received an additional blinded dose from Days 8 to 28 out of those receiving 300 mg in the double-blind period. Over the double-blind period, approximately half of the subjects with TRAPS or HIDS/MKD in the canakinumab group underwent a dose increase. Approximately 30% of the subjects with crFMF underwent a dose increase.

Table 13. Subjects in the canakinumab group who received an increased or additional dose during the double-blind period

	No dose increase	Dose increase	Subjects who underwent a dose increase and received an additional blinded dose from Days 8 to 28
TRAPS	50 (11/22)	50 (11/22)	36 (8/22)
HIDS/MKD	49 (18/37)	51 (19/37)	32 (12/37)
crFMF	68 (21/31)	32 (10/31)	16 (5/31)

% (number of subjects)

Table 14 shows the proportion of subjects who achieved remission in the primary analysis and in the exploratory analysis out of those initially randomized to the canakinumab group, and the proportion of subjects who received an additional dose from Days 8 to 28 and achieved index flare resolution. Table

15 shows the trend of the proportion of subjects with serological remission, and that with normalized SAA.

Table 14. Proportion of subjects achieving remission in the primary analysis and in the exploratory analysis out of subjects randomized to canakinumab, and the proportion of subjects who received an additional dose and achieved index flare resolution

	Subjects achieving remission		Subjects achieving index flare resolution after receiving an additional dose[a)]
	Primary analysis	Exploratory analysis	
TRAPS	45 (10/22)	73 (16/22)	63 (5/8)
HIDS/MKD	35 (13/37)	57 (21/37)	27 (4/15)
crFMF	61 (19/31)	71 (22/31)	60 (3/5)

% (number of subjects)

a) The proportion of subjects in the canakinumab group who received an additional dose from Days 8 to 28 and achieved index flare resolution not by Day 15 but by Day 29.

Table 15. Proportions of subjects achieving serological remission or normalized SAA in the canakinumab group

		Subjects achieving serological remission			Subjects achieving normalized SAA		
	Time assessed	Canakinumab	Canakinumab (No dose increase)	Canakinumab (Dose increase)	Canakinumab	Canakinumab (No dose increase)	Canakinumab (Dose increase)
TRAPS	Baseline	0	0	0	5 (1/22)	9 (1/11)	0
	Day 15	59 (13/22)	73 (8/11)	46 (5/11)	41 (9/22)	36 (4/11)	46 (5/11)
	Day 29	82 (18/22)	91 (10/11)	73 (8/11)	41 (9/22)	64 (7/11)	18 (2/11)
	After 16-week treatment	77 (17/22)	73 (8/11)	82 (9/11)	36 (8/22)	55 (6/11)	18 (2/11)
HIDS/MKD	Baseline	0	0	0	0	0	0
	Day 15	73 (27/37)	72 (13/18)	74 (14/19)	27 (10/37)	22 (4/18)	32 (6/19)
	Day 29	76 (28/37)	89 (16/18)	63 (12/19)	19 (7/37)	11 (2/18)	26 (5/19)
	After 16-week treatment	62 (23/37)	83 (15/18)	42 (8/19)	22 (8/37)	22 (4/18)	21 (4/19)
crFMF	Baseline	0	0	0	0	0	0
	Day 15	87 (27/31)	91 (19/21)	80 (8/10)	42 (13/31)	52 (11/21)	20 (2/10)
	Day 29	84 (26/31)	86 (18/21)	80 (8/10)	29 (9/31)	38 (8/21)	10 (1/10)
	After 16week treatment	94 (29/31)	100 (21/21)	80 (8/10)	26 (8/31)	38 (8/21)	0

% (number of subjects)

As shown, the proportion of subjects experiencing remission was higher in the exploratory analysis than in the primary analysis regardless of disease, and more than half of the subjects with other than HIDS/MKD who received an additional dose achieved index flare resolution. The results suggest the necessity of a dose increase to 300 mg or additional dose of 150 mg within 4 weeks and the presence of patients who would achieve remission by this regimen. At the same time, the proportion of subjects who underwent a dose increase from 150 mg to 300 mg canakinumab and achieved serological remission after 16-week treatment was lower in subjects with HIDS/MKD than in those with TRAPS or crFMF. The exploratory analysis revealed lower proportion of subjects experiencing remission in subjects with HIDS/MKD (57%) than in those with TRAPS (73%) or crFMF (71%). These results indicate the presence of patients with HIDS/MKD who require a further higher dose to achieve adequate benefit from canakinumab.

PMDA's view:

In Study N2301, approximately half of the patients with TRAPS or HIDS/MKD and approximately 30% of patients with crFMF underwent a dose increase by Week 16 of the treatment. As shown in Table 14, regardless of the primary disease (TRAPS, HIDS/MKD, or crFMF), the exploratory analysis that included subjects treated with an increased dose of 300 mg yielded high percentages of subjects with remission as compared to the primary analysis that was based on the data of subjects receiving 150 mg of canakinumab every 4 weeks. It is considered that patients who did not achieve remission after the treatment with 150 mg of canakinumab every 4 weeks may respond to 300 mg. However, the following findings indicate that the effect of dose increase to canakinumab 300 mg may be limited in patients with HIDS/MKD, suggesting the need of an even higher dose [see Section "7.R.5 Post-marketing investigations"].

- The proportion of patients in the canakinumab group with remission in the exploratory analysis was lower in HIDS/MKD patients than in TRAPS or crFMF patients.
- Among HIDS/MKD patients whose index flare did not resolve by the administration of 150 mg of canakinumab, the proportion of patients whose index flare resolved after dose increase to 300 mg was lower compared to that for TRAPS or crFMF.

7.R.2 Safety

7.R.2.1 Summary of safety

The applicant's explanation about the safety of canakinumab based on data from Study N2301 by primary disease and of all primary diseases combined, and the pooled data from 5 clinical studies (Studies D2308, D2304, A2102, D2306, and D2201) conducted in patients with CAPS in and outside Japan:

Table 16 is the summary of safety data of canakinumab from Study N2301 and 5 clinical studies in patients with CAPS. No obvious differences were observed between diseases.

Table 16. Summary of safety data of canakinumab from Studies N2301 and the 5 studies in patients with CAPS

	N2301								CAPS Pooled (n = 194)
	Double-blind period							HPF Combined Canakinumab [b] (n = 193)	
	TRAPS[a] (n = 46)		MKD/HIDS[a] (n = 72)		crFMF[a] (n = 63)		HPF Combined Canakinumab (n = 169)		
	Canakinumab	Placebo	Canakinumab	Placebo	Canakinumab	Placebo			
Total exposure period (patient years)	12.10	2.00	19.11	2.95	16.41	3.08	47.61	135.81	289.33
Study drug treatment period[c] (days)	102.8 [28, 127]	30.5 [7, 116]	102.6 [11, 128]	30.8 [7, 119]	103.3 [37, 129]	35.2 [7, 116]	102.9 [11, 129]	257.0 [45, 391]	544.7 [29, 1884]
Death	0	0	0	0	0	0	0	0	0
Serious adverse event	3 24.8	1 50.0	11 57.6	4 135.5	7 42.7	3 97.4	21 44.1	42 30.9	46 15.9
Adverse event leading to treatment discontinuation	0	0	2 10.5	1 33.9	0	0	2 4.2	8 5.9	7 2.4
Adverse reaction	25 206.6	2 99.9	42 219.8	12 406.6	37 225.5	7 227.3	104 218.4	218 160.5	245 84.7
Adverse event	112 925.7	28 1399.0	251 1313.6	56 1897.4	134 816.7	52 1688.3	497 1043.8	1210 890.9	1985 686.1
Infection	26 214.9	3 149.9	72 376.8	7 237.2	28 170.6	9 292.2	126 264.6	297 218.7	563 194.6
Opportunistic infection	0	0	0	0	0	0	0	0	0
Neutropenia	2 16.5	0	1 5.2	3 101.6	0	0	3 6.3	6 4.4	3 1.0

Upper row, number of cases; lower row, total exposure-adjusted incidence rate per 100 patient-years

[a] Calculated by study drug which was administered at the onset of occurrence of the adverse event

[b] Data from the double-blind period (up to Week 16) and the withdrawal/treatment interval extension period (up to Week 40)

[c] Mean value [minimum, maximum]

A comparison between canakinumab and placebo administered during the double-blind period revealed no trend toward increasing incidences of serious adverse events associated with canakinumab. The only serious adverse event that occurred in ≥2 subjects during the double-blind period associated with canakinumab was pneumonia (2 subjects). A causal relationship to canakinumab was ruled out and its outcome in either subject was "resolved." There were no new serious adverse events that occurred in ≥2 subjects during the withdrawal/treatment interval extension period. Furthermore, data of patients with hereditary periodic fevers (HPF) combined and pooled data of patients with CAPS were compared for the risk of infections including opportunistic infection and neutropenia. Both were considered as risks of special concern due to the pharmacological action of canakinumab and their incidence in patients with CAPS. In light of the different duration of total exposure, the 2 data sets have no significant difference by primary disease.

Based on the above, there is no significant difference in the trend of incidence of adverse events among patients with TRAPS, HIDS/MKD, and crFMF. No significant difference was suggested in the safety profile of canakinumab in patients with TRAPS, HIDS/MKD, or crFMF as compared with that in the patients treated for the approved indications.

Furthermore, due to the extremely small number of Japanese subjects (8) who received canakinumab in Study N2301, the applicant explained the safety of canakinumab in the Japanese population based on

the safety data from post-marketing surveillance targeting all patients with CAPS treated with canakinumab as follows:
As of December 31, 2015, 84 patients had been registered in the post-marketing surveillance. Of 58 patients of whom data up to Week 24 were finalized, 1 patient was excluded because of off-label use, and the remaining 57 patients were included in the safety analysis population.

Adverse events and adverse drug reactions occurred in 47 of 57 patients (83%), and 15 of 57 patients (26%), respectively. Adverse drug reactions that occurred in ≥2 patients were nasopharyngitis (3), upper respiratory tract infection (3), skin infection (2), and upper respiratory tract inflammation (2). Serious adverse events occurred in 6 of 57 patients (11%), and the events that occurred in ≥2 patients were bronchitis (2). All serious adverse events improved or resolved, and no adverse events led to treatment discontinuation. No safety-related problems were reported in patients included in the safety analysis population who received canakinumab at ≥450 mg (or 6 mg/kg for patients weighing ≤40 kg).

Based on the above, drugs that may be used for periodic fever syndromes are steroids, non-steroidal anti-inflammatory drugs, colchicine, and immunosuppressants, and these are common to TRAPS, HIDS/MKD, FMF, and CAPS. Canakinumab is thus unlikely to cause new safety concerns when administered to Japanese patients with TRAPS, HIDS/MKD, or FMF.

PMDA's view:
The safety of canakinumab in the treatment of TRAPS, HIDS/MKD, or crFMF is comparable to that in use for the approved indications based on the incidences of adverse events and safety profile of canakinumab. However, due to extremely limited experience in the use of canakinumab in Japanese patients with TRAPS, HIDS/MKD, or crFMF, data collection via post-marketing surveillance and further investigation on the occurrence of adverse events including serious infections based on the collected data are essential.

7.R.2.2 Safety by age group

The applicant's explanation about the safety of canakinumab by age group based on the HPF data from Study N2301, safety data of 2 patients with HIDS/MKD aged <2 years in the non-randomized group, and results of a foreign study, Study D2307, conducted in patients with CAPS aged ≥28 days and ≤4 years:
Table 17 shows major adverse events by age group revealed by the combined data of HPF patients from Study N2301. The subgroups of age 6 to 11 years, 12 to 17 years, and 18 to 64 years had relatively large population. Adverse events occurring at a ≥5%-higher rate in any of these subgroups than in the entire population were pyrexia and abdominal pain (both age 6 to 11 years), upper respiratory tract infection (age 12 to 17 years), and injection site reaction (age 18 to 64 years). The incidences of other events were comparable between the whole group and the respective subgroups. A similar analysis using CAPS pooled data revealed that adverse events occurring at a ≥5%-higher rate in any of the age subgroups than

in the entire population were diarrhoea (age 6 to 11 years and 12 to 17 years), pyrexia, headache, oropharyngeal pain, and upper respiratory tract infection (age 6 to 11 years), nasopharyngitis, and arthralgia (age 12 to 17 years). Age group-based safety profiles in the combined HPF patient data and the CAPS pooled data were generally similar.

Table 17. Incidences of adverse events that was ≥10% in HPF patients in the canakinumab groups of Study N2301 by age group (data cut-off on Week 16[a])

	2 to 3 years (n = 9)	4 to 5 years (n = 17)	6 to 11 years (n = 36)	12 to 17 years (n = 40)	18 to 64 years (n = 65)	≥65 years (n = 2)	Total (n = 169)
Adverse events total	8 (89)	15 (88)	31 (86)	31 (78)	54 (83)	2 (100)	141 (83)
Pyrexia	2 (22)	5 (29)	17 (47)	5 (13)	7 (11)	0	36 (21)
Headache	0	4 (24)	6 (17)	9 (23)	10 (15)	1 (50)	30 (18)
Diarrhoea	1 (11)	4 (24)	4 (11)	5 (13)	7 (11)	1 (50)	22 (13)
Abdominal pain	0	1 (6)	7 (19)	4 (10)	9 (14)	0	21 (12)
Injection site reaction	1 (11)	1 (6)	3 (8)	3 (8)	13 (20)	0	21 (12)
Nasopharyngitis	2 (22)	0	4 (11)	5 (13)	7 (11)	0	18 (11)
Oropharyngeal pain	0	1 (6)	5 (14)	4 (10)	8 (12)	0	18 (11)
Upper respiratory tract infection	2 (22)	1 (6)	2 (6)	7 (18)	5 (8)	0	17 (10)
Arthralgia	0	3 (18)	4 (11)	2 (5)	8 (12)	0	17 (10)

Number of subjects (%)

[a] Data obtained by the cut-off date for the Week 16 interim summary including those obtained during and after the withdrawal/treatment interval extension period

Serious hepatic failure and pancytopenia occurred in 1 of the 2 patients with HIDS/MKD aged <2 years in the non-randomized group of Study N2301 [see Section "7.R.2.3 Liver disorder"]. A causal relationship to the study drug could not be ruled out for these events, and treatment with the study drug was discontinued. This subject had abnormal hepatic function and iron deficiency anemia before the start of the study and a history of immune thrombocytopenic purpura.

Data of patients with CAPS aged 28 days to 4 years were not included in the CAPS pooled data. Study D2307,[14] a foreign study, was conducted in patients with CAPS in this age group, and 17 subjects (6 subjects aged 1 to 23 months, and 11 subjects aged 2 to 4 years) received canakinumab. All subjects experienced adverse events, many of which were related to infections, and the study yielded a safety profile similar to that in previous clinical studies of canakinumab. Serious adverse events occurred in 4 subjects (influenza/lung infection/cryopyrin associated periodic syndrome [1], diarrhoea/vomiting [1], cryptorchism/wound infection staphylococcal [1], and femur fracture [1]). All the subjects recovered following dose interruption or reduction or symptomatic treatment. There were no problems in terms of the safety or tolerability of canakinumab.

[14] An open-label uncontrolled study which enrolled 12 patients with Muckle-Wells syndrome, 4 patients with neonatal-onset multisystem inflammatory disease, 1 patient with familial cold autoinflammatory syndrome. The starting dose was 2 mg/kg (4 mg/kg for patients with neonatal-onset multisystem inflammatory disease) every 8 weeks, and the dose was able to be increased up to 8 mg/kg every 4 weeks in case of inadequate response.

The above results indicate that the safety of canakinumab in young pediatric patients does not differ greatly from that of other age groups, suggesting no safety concerns specific to the younger age group.

PMDA's view:
The safety evaluation of canakinumab in the younger age group is constrained by limited experience in its use in the age group. The data submitted suggest no trend toward an increased risk associated with canakinumab in specific age groups. Nevertheless, only 1 young Japanese pediatric patient with TRAPS, 1 with HIDS/MKD, and 4 with CAPS have been treated with canakinumab, and, therefore, the safety of canakinumab should be further investigated in specific patient groups such as younger pediatric patients via post-marketing surveillance.

7.R.2.3 Liver disorder
A serious hepatic failure occurred in 1 Japanese patient with HIDS/MKD aged 1 year, and a causal relationship to the study drug could not be ruled out for the event.

The applicant's explanation about the risk of liver disorder:
In Study N2301, the incidence of liver disorder-related events during the double-blind period and withdrawal/treatment interval extension period was 2.6% (5 of 193 subjects; 1 with TRAPS, 3 with HIDS/MKD, and 1 with crFMF) in HPF patients in the canakinumab groups. These events were, namely, alanine aminotransferase increased (3), aspartate aminotransferase increased (2), ascites (1), hepatic cirrhosis (1), granulomatous liver disease (1), gamma-glutamyltransferase increased (1), and hepatic failure (1). A causal relationship to the study drug was ruled out for all events except granulomatous liver disease and hepatic failure. Treatment discontinuation or dose interruption or reduction was performed only in the patient experienced hepatic failure. All events except hepatic cirrhosis and granulomatous liver disease resolved by the end of the withdrawal/treatment interval extension period. Accordingly, the risk of drug-induced liver disorder following the administration of canakinumab was considered low.

PMDA asked the applicant to explain the clinical course and cause of hepatic failure in the Japanese patient with HIDS/MKD aged 1 year in the non-randomized group in Study N2301.

The applicant's explanation:
The subject tested negative for major causative viruses of hepatitis including hepatitis B at screening, and therefore hepatic failure seemed unlikely to have been caused by virus infection. Liver disorder is a known adverse reaction of some of the concomitant drugs. However, the possibility is low that hepatic failure was caused by the concomitant drugs in light of the starting date and treatment period with the drugs and the trend in liver function test results. The possibility that hepatic failure was caused by canakinumab could not be ruled out because of, albeit rare, the onset of canakinumab-induced liver disorder and its onset date, which was 16 days after the first dose.

Prior to the start of study drug treatment, the subject had abnormal liver function and decreased platelet count and was diagnosed to have concomitant hepatic dysfunction and a history of immune thrombocytopenic purpura. Literature on HIDS/MKD patients with liver disorders reported on complications associated with hepatitis including suspected cases, advanced liver disorder requiring liver transplant, and decreased platelet count, and some were similar to the case of the subject in Study N2301 (e.g., *Am J Transplant.* 2012;12:1627-31, *Am J Med Genet.* 1998;78:408-12). As suggested by the literature, it is also possible that the subject's liver disorder was progressed by a flare of HIDS/MKD, the subject's primary disease, leading to hepatic failure.

Based on the above, while the possibility remains that hepatic failure of the subject was caused by canakinumab, it may be attributable to the primary disease/previous disease or complication of the subject.

PMDA's view:
The possibility remains that serious hepatic failure in the Japanese HIDS/MKD patient in Study N2301 was caused by canakinumab because the event occurred after the start of canakinumab treatment. On the other hand, abnormal liver function test results and decreased platelet count were noted in the subject prior to the start of canakinumab treatment. Published literature reported on complications associated with serious hepatic failure and platelet count decreased with a similar clinical course to that in the subject with HIDS/MKD in Study N2301. These observations preclude a definitive conclusion that canakinumab is the causative drug of hepatic failure in the subject. The incidence of liver disorder-related adverse events was low in patients with HPF in Study N2301, and the total exposure-adjusted incidence of drug-induced liver disorder per 100 patient-years is as low as 0.65 based on the post-marketing safety data in Japan and from overseas. However, the hepatic failure was a serious event and required plasma exchange and liver transplantation after canakinumab was discontinued. Therefore, the association between canakinumab and liver disorder should be further investigated via post-marketing surveillance.

7.R.3 Clinical positioning and indications
The applicant's explanation about the clinical positioning of canakinumab:
TRAPS, HIDS, and FMF are hereditary autoinflammatory diseases with periodic recurrence of pyrexia (≥38°C), accompanying symptoms including serositis, neutrophilic rash, mucosal ulceration, arthralgia/arthritis, and meningitis aseptic/headache. Systemic inflammatory attacks with high fever affect the patient's daily activities and necessitate hospitalization for treatment, consequently severely compromising the patient's quality of life. Despite that, no drugs have been approved for the treatment of TRAPS and HIDS/MKD in Japan or overseas. Colchicine is recommended as standard treatment for FMF. While colchicine has been approved in Japan for the indication of FMF, high doses of colchicine cause adverse reactions such as diarrhoea, abdominal pain, and vomiting and are of concern.

Furthermore, approximately 10% of patients are colchicine-resistant or intolerant, and there is no established therapy for these patients. To alleviate fever and accompanying symptoms in patients with TRAPS, HIDS/MKD, or FMF, non-steroidal anti-inflammatory drugs, oral anti-inflammatory drugs (e.g., acetaminophen), and adrenocortical steroids are used. However, these drugs have limited effect to prevent flares and shorten an attack.

One of the clinically critical issues for TRAPS, HIDS/MKD, and FMF is to control attacks and to improve systemic inflammation to prevent amyloidosis, which influences the long-term prognosis. The effects of canakinumab in the suppression of flare recurrence and normalization of inflammation markers such as CRP and SAA are important benefits for patients with TRAPS, HIDS/MKD, and crFMF. The efficacy of canakinumab has already been demonstrated in the treatment of TRAPS, HIDS/MKD, and crFMF and its safety has also been confirmed. Therefore, canakinumab may be an effective therapeutic option for patients who are in need of novel therapy.

PMDA's view:
As explained by the applicant, the data submitted and discussions in Sections "7.R.1 Efficacy" and "7.R.2 Safety," indicate that canakinumab can be a new treatment option for patients with TRAPS or HIDS/MKD, for whom there are no treatments with established efficacy. In contrast, in the treatment of FMF, canakinumab should be as a treatment option for patients who are inadequately responding or intolerant to colchicine for the following reasons:

- The clinical guidelines used in Japan and overseas mention colchicine as the standard treatment option for patients with FMF. One of the diagnostic criteria for FMF is the disappearance or alleviation of attacks after oral prophylactic administration (*Ann Rheum Dis.* 2016;75:644–51, *Health Labour Sciences Research Grant: Research on Measures for Intractable Diseases "Elucidation of pathology of familial Mediterranean fever, and establishment of treatment guidelines," FY2011 to 2012, Comprehensive Research Report*, 2013;15-21)
- Inhibition of IL-1β by canakinumab may affect immune response, and therefore canakinumab has a risk for infections
- FMF patients enrolled in Study N2301 were refractory or intolerant to colchicine, and the efficacy of canakinumab was demonstrated in these patients

In clinical practice, both "hyperimmunoglobulin D syndrome" and "mevalonate kinase deficiency" are used to refer to the same disease because some patients with HIDS/MKD do not have increased IgD, and it has been suggested that the nature of the disease is the reduced activity of mevalonate kinase. Considering this situation and the specified intractable disease term, it is appropriate to specify the indications for canakinumab as "tumor necrosis factor receptor associated periodic syndrome, hyperimmunoglobulin D syndrome (mevalonate kinase deficiency), and familial Mediterranean fever refractory to conventional treatment."

7.R.4 Dosage and administration

The applicant's explanation about the dosage and administration of canakinumab:

In Study N2301, the superiority of canakinumab 150 mg every 4 weeks over placebo was demonstrated [see Section "7.R.1.2 Efficacy at the starting dose and dosage regimen"], and subjects inadequately responding to canakinumab 150 mg achieved remission after a dose increase to 300 mg every 4 weeks [see Section "7.R.1.3 Efficacy after dose increase"]. Accordingly, the starting dose of canakinumab should be 150 mg every 4 weeks, allowing an increase to 300 mg every 4 weeks for patients with inadequate response. On the other hand, it was suggested that a greater number of patients with HIDS/MKD have difficulty in disease control than patients with TRAPS or crFMF even by canakinumab 300 mg. Accordingly, the efficacy of canakinumab 450 mg was evaluated based on the results from Study D2402, a foreign study in patients with HIDS/MKD treated with canakinumab 450 mg, and a clinical research on 1 Japanese patient with HIDS/MKD treated with canakinumab 6 mg/kg.

In Study D2402, canakinumab 300 mg was administered every 6 weeks by subcutaneous injection. Patients with inadequate response received an increased dose of 450 mg (or 6 mg/kg for patients weighing ≤40 kg). This open-label uncontrolled study aimed to evaluate the efficacy and safety of canakinumab after dose increase, and 2 of 9 subjects enrolled in the study received canakinumab 450 mg. Table 18 shows the clinical courses of the subjects, indicating a certain degree of efficacy of canakinumab 450 mg.

Table 18. Number of flares, CPR, and SAA levels in subjects who received canakinumab 450 mg or 6 mg/kg in Study D2402

	Dose increase	Number of flares[a)]			CRP and SAA levels	
					CRP (mg/L)	SAA (mg/L)
Females (aged 7 years)	6 mg/kg (Day 45)	6 months before the start of treatment[b)]	9	Day 1	86.3	627
		6 months after the start of treatment	2[c)]	Day 45	12.1	
		7 to 18 months after the start of treatment	3	Week 24	0.9	2.8
		19 to 30 months after the start of treatment	1	Week 48	0.8	3.3
Males (aged 20 years)	450 mg (Day 45)	6 months before the start of treatment[b)]	4	Day 1	112	
		6 months after the start of treatment	1[d)]	Day 45	0	
		7 to 18 months after the start of treatment	0	Week 24	0	
		19 to 30 months after the start of treatment	0	Week 48	1	

[a)] Definition of flare: physician's global assessment of mild, moderate, or severe and CRP >10 mg/L

[b)] The latest 6 months during which no other drugs were used except for adrenocortical steroids or non-steroidal anti-inflammatory drugs for symptomatic treatment

[c)] During the time of flare, the physician's global assessment, CRP level, and SAA level were: moderate, 72.4 mg/L, and 1500 mg/L for the first flare during the period; and mild, 8.6 mg/L, and 58.2 mg/L for the second flare during the period, respectively.

[d)] The physician's global assessment and CRP level at the time of flare were mild and 2 mg/L, respectively.

The clinical course of a patient with severe HIDS/MKD who was refractory to anakinra in the clinical research was as follows:

- The patient received canakinumab 2 mg/kg initially, and an additional dose of canakinumab 2 mg/kg was administered 7 days later because CRP did not improve. After the additional administration, the rating of the physician's global assessment and CRP level improved; therefore, treatment was continued with 4 mg/kg every 4 weeks. The first new flare occurred for the first time after approximately 1 year of treatment, and the patient was hospitalized. After ≥2 years from the start of the treatment with canakinumab, the dose was increased to 6 mg/kg, and the improved symptoms was maintained for 1 year after dose increase.

PMDA asked the applicant to explain the rationale for the decision to increase the dose of canakinumab to 450 mg every 4 weeks only in HIDS/MKD patients from the perspectives of the difference in pathology, disease activity, and IL-1β production between HIDS/MKD and TRAPS or FMF.

The applicant's explanation:
Despite their different causative genes, TRAPS, HIDS/MKD, FMF, and CAPS are all classified as periodic fever syndromes and are hereditary autoinflammatory diseases caused by anomalies in IL-1β production. These diseases are known to develop at the age of <20 years, except HIDS/MKD that develops at the age of <1 year. In patients with mevalonic aciduria, a severe form, progressive cerebellar ataxia and developmental disorder are observed, indicating a potentially unfavorable long-term prognosis.

Based on the results from Study N2301, the difference in IL-1β production among the diseases was studied. The serum concentration of IL-1β at baseline was higher in HIDS/MKD subjects than in TRAPS or crFMF subjects (Figure 3), and therefore it was considered that a higher dose would be required in HIDS/MKD patients to neutralize IL-1β. In Study N2301, the number of subjects receiving the increased dose of 300 mg were 13 of 46 TRAPS subjects (28%), 31 of 72 HIDS/MKD subjects (43%), and 15 of 63 crFMF subjects (24%). Of those treated with the increased dose, 6 of 46 TRAPS subjects, 20 of 72 HIDS/MKD subjects, and 5 of 63 crFMF subjects experienced a flare.

The above results suggested the possibility that some patients with any of the primary diseases fail to respond adequately to canakinumab 300 mg and present with a new flare. This trend was seen particularly in patients with HIDS/MKD patients than in those with other diseases. Therefore, the maximum dose of 450 mg is appropriate for patients with HIDS/MKD.

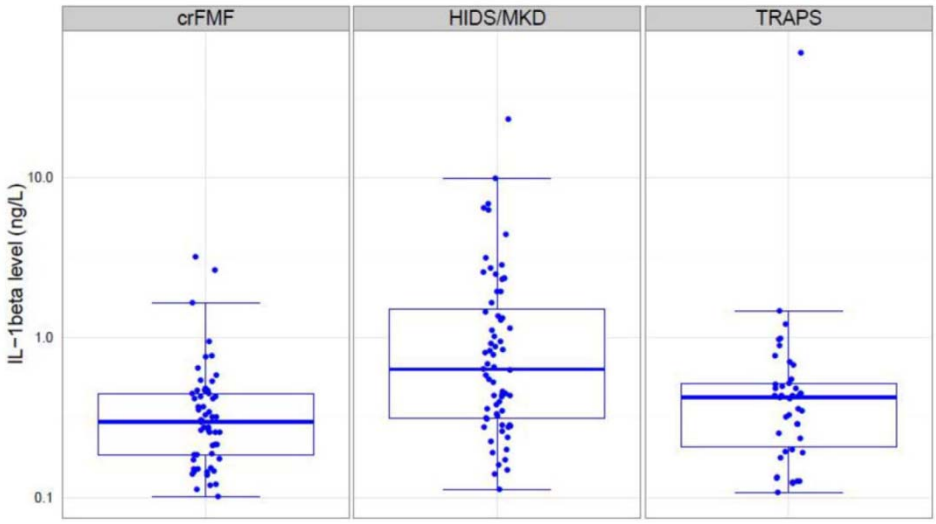

Figure 3. Baseline serum IL-1β concentrations in Study N2301

PMDA's view:

Based on the discussion in "7.R.1 Efficacy," it was concluded that the dosage and administration of canakinumab can be specified as follows for patients with TRAPS, HIDS/MKD, or crFMF, as proposed by the applicant: The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg, and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 4 weeks. The doses may be increased to 4 mg/kg and 300 mg, respectively, for patients not achieving adequate clinical response. The serum concentration of IL-1β was higher in patients with HIDS/MKD than in those with TRAPS or crFMF, and the proportions of subjects who underwent a dose increase to 300 mg and those who had a new flare following the dose increase were high in patients with HIDS/MKD in Study N2301. Therefore, the applicant's explanation about the need of a higher dose for patients with HIDS/MKD is reasonable. In foreign clinical studies and a Japanese clinical research, there were HIDS/MKD patients, albeit few in number, in whom disease activity was suppressed by the dose increased to 450 mg every 4 weeks. In Japan, up to 600 mg of canakinumab can be administered to patients with CAPS every 4 weeks. Post-marketing safety data on canakinumab at ≥450 mg in patients with CAPS has raised no safety concerns. Given these, the upper limit of 450 mg is acceptable due to concerns of long-term prognosis of HIDS/MKD that develops at young ages and may cause developmental disorder with a possible fatal outcome in its severe form in infants.

The above conclusion by PMDA will be discussed in the Expert Discussion.

7.R.5 Post-marketing investigations

There is no clear difference in the safety profile of canakinumab between patients with TRAPS, HIDS/MKD, and crFMF and patients with CAPS. However, due to the small number of Japanese patients with TRAPS, HIDS/MKD, or crFMF evaluated in the clinical study and the limited data on clinical use of canakinumab at 450 mg in patients with HIDS/MKD, it is necessary to conduct post-marketing surveillance covering all patients receiving canakinumab to continue investigating the safety

and efficacy of canakinumab carefully in patients with TRAPS, HIDS/MKD, or crFMF in actual use. The use of canakinumab must be determined by a physician with adequate knowledge and experience in the diagnosis and treatment of TRAPS, HIDS/MKD, and crFMF, in view of its benefits and risks, and the proper use of canakinumab must be observed. Therefore, the same safety measures should be taken as in the use for the approved indication.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion on the results of GCP on-site inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of Review Report (1)

On the basis of data submitted, PMDA has concluded that canakinumab has efficacy in the treatment of TRAPS, HIDS/MKD, and crFMF, and that canakinumab has acceptable safety in view of its benefits. Currently, only colchicine is available for the indication of FMF and there are no other effective treatments in Japan. Canakinumab will provide a new treatment option for these diseases and is of clinical significance. Only the small number of Japanese patients with TRAPS, HIDS/MKD, or crFMF were evaluated in the clinical study, and extremely few patients with HIDS/MKD were treated with canakinumab 450 mg. Because of its action mechanism, canakinumab may cause serious adverse events including serious infections. Therefore, the safety and efficacy of canakinumab in post-marketing use in patients with TRAPS, HIDS/MKD, or crFMF should be further investigated carefully through post-marketing surveillance covering all patients receiving canakinumab.

PMDA has concluded that canakinumab may be approved if canakinumab is considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 15, 2016

Product Submitted for Approval

Brand Name	Ilaris for S.C. Injection 150 mg
Non-proprietary Name	Canakinumab (Genetical Recombination)
Applicant	Novartis Pharma K.K.
Date of Application	April 25, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1. Efficacy, Indications, and Dosage and Administration

The conclusions of PMDA concerning the efficacy, indications, and dosage and administration of Ilaris for S.C. Injection 150 mg described in Review Report (1) were supported by the expert advisors at the Expert Discussion.

1.2. Safety, and Risk Management Plan (Draft)

At the Expert Discussion, an expert advisor made the following comment on the safety of canakinumab and the post-marketing safety measures described in Review Report (1). The expert advisors supported the PMDA's conclusion.

- According to the applicant, serious hepatic failure and pancytopenia that occurred in a patient with hyper IgD syndrome (mevalonate kinase deficiency) aged <2 years may be attributable to the primary disease of the patient. Although the applicant's explanation is acceptable at present, data collection should be continued and cautions should be given as necessary in the post-marketing setting.

PMDA's conclusions:

Based on the decisions in Section "7.R.5 Post-marketing investigations" of Review Report (1) and the discussions at the Expert Discussion, the safety and efficacy specifications for the current risk

management plan (draft) for canakinumab should be specified as summarized in Table 19. Additional pharmacovigilance and risk minimization activities should be implemented (Table 20).

Table 19. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infections (including opportunistic infection) • Neutrophil count decreased	• Shock, anaphylaxis • Malignant tumor • Liver dysfunction	• Not applicable
Efficacy specification		
• Efficacy in the treatment of familial Mediterranean fever refractory to conventional treatment, tumor necrosis factor receptor associated periodic syndrome, and hyperimmunoglobulin D syndrome (mevalonate kinase deficiency) in routine clinical use		

Table 20. Summary of additional pharmacovigilance and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use results survey[a)] (all case surveillance) • Use results survey[b)] (all case surveillance)	• Early post-marketing phase vigilance • Creation and distribution of materials for those engaged in clinical practice • Ensuring that information on proper use should be provided before the delivery of the product

a) Survey in patients with cryopyrin-associated periodic syndromes
b) Survey in patients with familial Mediterranean fever refractory to conventional treatment, tumor necrosis factor receptor associated periodic syndrome, and hyperimmunoglobulin D syndrome (mevalonate kinase deficiency)

PMDA further instructed the applicant to conduct post-marketing surveillance to investigate the above items.

The applicant's explanation about a use-results survey (Table 21):

- The survey will target patients with familial Mediterranean fever refractory to conventional treatment, tumor necrosis factor receptor associated periodic syndrome, and hyperimmunoglobulin D syndrome (mevalonate kinase deficiency) with an observation period of 2 years. The survey will cover all patients receiving canakinumab during the observation period.
- Key survey items are infection (including opportunistic infection), neutrophil count decreased, shock/anaphylaxis, malignant tumor, and hepatic dysfunction. The safety and efficacy of canakinumab in routine clinical use will be investigated.
- After the completion of the observation period, patients who continue to receive canakinumab will be followed for up to 5 years after the start of treatment. The follow-up will focus on symptoms that may affect patients' physical functions and vital prognosis as well as the occurrence of serious infections and malignant tumors to further investigate the safety of canakinumab in long-term use.

Table 21. Outline of use-results survey (draft)

Objective	To verify safety and efficacy of canakinumab in long-term routine use
Survey method	Central registry system
Target patients	Familial Mediterranean fever refractory to conventional treatment, tumor necrosis factor receptor associated periodic syndrome, and hyperimmunoglobulin D syndrome (mevalonate kinase deficiency)
Observation period	2 years (After the completion of the observation period, a follow-up survey should be conducted in patients continue receiving canakinumab for up to 5 years after the start of treatment.)
Planned sample size	All patients receiving canakinumab
Main survey items	• Key survey items: infections (including opportunistic infection), neutrophil count decreased, shock/anaphylaxis, malignant tumor, and hepatic dysfunction • Patient characteristics (e.g., height, body weight, symptoms and duration of primary disease, diagnostic information for the primary disease, complications, and medical history) • Treatment history • Current status of the treatment with canakinumab • Concomitant drugs/therapy • Laboratory tests • Adverse events • Efficacy evaluation

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication, and dosage and administration modified as shown below, with the following conditions. Canakinumab is designated as an orphan drug for the indications proposed in the current application. The re-examination period for the indications and the dosage and administration proposed in the current application is 10 years.

Indications

1.The following c~~C~~ryopyrin-associated periodic syndromes~~:~~

• Familial cold autoinflammatory syndrome~~,~~

• Muckle-Wells syndrome~~, and~~

• ~~n~~Neonatal-onset multisystem inflammatory disease

2. Familial Mediterranean fever refractory to conventional treatment

3. Tumor necrosis factor (TNF) receptor-associated periodic syndrome

4. ~~Mevalonate kinase deficiency/h~~Hyperimmunoglobulin D syndrome (mevalonate kinase deficiency)

(Strike-through denotes deletion and underline addition.)

Dosage and administration

Cryopyrin-associated periodic syndromes

The usual dosage of canakinumab (genetical recombination) is at 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 8 weeks.

Patients not achieving adequate clinical response (resolution of rash and other generalized inflammatory symptoms) may receive a gradually increased dose as needed. However, the maximum dose is 8 mg/kg for patients with a body weight of ≤40 kg and 600 mg for patients with a body weight of >40 kg.

If a disease flare occurs within 8 weeks of treatment at a maximum dose, the dose interval may be shortened to not less than 4 weeks.

The dose should be adjusted according to the patient's condition.

Familial Mediterranean fever and tumor necrosis factor (TNF) receptor-associated periodic syndrome
The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients with a body weight of >40 kg administered by subcutaneous injection every 4 weeks.

Patients not achieving adequate clinical response may receive an additional dose or gradually increased dose as needed.~~, another dose can be administered as needed 7 days after administration or later: at 2 mg/kg for patients with a body weight of ≤40 kg, and 150 mg for patients with a body weight of >40 kg. Also, as a general rule, from the next dose 4 weeks later, the dose should be increased to 4 mg/kg for patients with a body weight of ≤40 kg, and 300 mg for patients with a body weight of >40 kg~~.

~~The dose per administration should be adjusted according to the patient's condition; however, the maximum dose should not exceed.~~ However, the maximum dose is 4 mg/kg for patients with a body weight of ≤40 kg and 300 mg for patients with a body weight of >40 kg.

~~Mevalonate kinase deficiency/h~~Hyperimmunoglobulin D syndrome (mevalonate kinase deficiency)
The usual dosage of canakinumab (genetical recombination) is 2 mg/kg for patients with a body weight of ≤40 kg and 150 mg for patients witha body weight of >40 kg administered by subcutaneous injection every 4 weeks.

Patients not achieving adequate clinical response may receive an additional dose or gradually increased dose as needed.~~, another dose can be administered as needed 7 days after administration or later: at 2 mg/kg for patients with a body weight of ≤40 kg, and 150 mg for patients with a body weight of >40 kg. Also, as a general rule, from the next dose 4 weeks later, the dose should be increased to 4 mg/kg for patients with a body weight of ≤40 kg, and 300 mg for patients with a body weight of >40 kg.~~

~~If a satisfactory clinical response has not been achieved after increasing the dose, another dose can be administered as needed 7 days after the increased dose or later: at 2 mg/kg for patients with a body weight of ≤40 kg, and 150 mg for patients with a body weight of >40 kg. Also, as a general rule, from~~

~~the next dose 4 weeks later, the dose should be increased to 6 mg/kg for patients with a body weight of ≤40 kg, and 450 mg for patients with a body weight of >40 kg.~~

~~The dose per administration shouold be adjusted according to the patient's condition; however, the maximum dose should not exceed.~~ However, the maximum dose is 6 mg/kg for patients with a body weight of ≤40 kg and 450 mg for patients with a body weight of >40 kg.

(Strike-through denotes deletions and underline addition.)

Conditions of approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the extremely limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct post-marketing surveillance on the safety and efficacy of the product covering all patients treated with the product throughout the re-examination period or until data of a specific number of patients are collected. The safety and efficacy of the drug product in its long-term use, including the occurrence of infections, should be carefully evaluated based on the data collected.