Arthritis & Rheumatology
Vol. 76, No. 2, February 2024, pp 304–312
DOI 10.1002/art.42695

American College of Rheumatology
Empowering Rheumatology Professionals

Long-Term Efficacy and Safety of Canakinumab in Patients With Tumor Necrosis Factor Receptor–Associated Periodic Syndrome: Results From a Phase III Trial

Marco Gattorno,[1] Laura Obici,[2] Inmaculada Calvo Penadés,[3] Tilmann Kallinich,[4] Susanne Benseler,[5] Elise Dekker,[6] Jérémy Lévy,[6] Fabrizio De Benedetti,[7] and Helen Lachmann[8]

Objective. We aimed at assessing efficacy, safety, and tolerability of canakinumab in patients with tumor necrosis factor receptor–associated periodic syndrome (TRAPS) during a 72-week long-term, open-label extension of the CLUSTER study.

Methods. Patients received open-label canakinumab 150 or 300 mg, either every 4 weeks (q4w) or every 8 weeks, with up-titration permitted after on-treatment flares (maximum dose: 300 mg q4w). Efficacy assessments included physician global assessment of disease activity, number of flares, and serum C-reactive protein (CRP) and serum amyloid A protein (SAA) levels. Adverse events were also reported. Results are described for the overall population and according to the cumulative dose of canakinumab adjusted for body weight (<36 mg/kg or ≥36 mg/kg).

Results. Of 53 patients entering the final phase (epoch 4) of CLUSTER, 51 completed the treatment. At the end of epoch 4, >94% of patients achieved no or minimal disease activity. Most patients had either no (69.8%) or one flare (24.5%), whereas at baseline, the median number of flares was 9.0 per year. Median CRP levels remained at <10 mg/L. Median SAA concentrations were largely unchanged, with medians of 11.5 mg/L and 14.5 mg/L in the <36 mg/kg and ≥36 mg/kg groups, respectively, at the end of the study. No unexpected safety findings were identified.

Conclusion. Control of disease activity, with low flare incidence, was maintained with long-term canakinumab treatment in patients with TRAPS during the 72-week final epoch of the CLUSTER study, with no new safety findings.

INTRODUCTION

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is an autoinflammatory hereditary disease characterized by attacks of fever that typically last between 10 and 14 days, associated with serositis, rash, and arthralgia or myalgia.[1] Onset is mostly during early childhood, and laboratory features typical of TRAPS during febrile episodes include elevated acute phase reactants, leukocytosis, and thrombocytosis.[2–4] Amyloid A amyloidosis is the most serious long-term complication of TRAPS and can lead to renal failure and death.[5]

TRAPS is caused by inherited mutations in the *TNFRSF1A* gene, which encodes tumor necrosis factor (TNF) receptor type 1 (TNFR1).[1] TNFR1 is located on the surface of most cells and is often involved in the initiation of an inflammatory response during infection. Mutations of TNFR1 cause protein misfolding and retention in the endoplasmic reticulum, causing an unfolded protein response and leading to increased proinflammatory signaling, impaired autophagy, and increased production of TNF, interleukin-1β (IL-1β), and IL-6.[6,7]

The clinical manifestations of TRAPS can be controlled using nonsteroidal antiinflammatory drugs, corticosteroids, and biologics,[8] but the 2012 Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations for the

ClinicalTrials.gov identifier: NCT02059291.
EudraCT number: 2013-004291-35.
Supported by Novartis Pharma AG.

[1]Marco Gattorno, MD: IRCCS Giannina Gaslini Institute, Genoa, Italy; [2]Laura Obici, MD: IRCCS Policlinico San Matteo Foundation, Pavia, Italy; [3]Inmaculada Calvo Penadés, MD: La Fe University and Polytechnic Hospital, Valencia, Spain; [4]Tilmann Kallinich, MD: Charité Universitätsmedizin Berlin and Deutsches Rheumaforschungszentrum, Berlin, Germany; [5]Susanne Benseler, MD: Alberta Children's Hospital, University of Calgary, Alberta, Canada; [6]Elise Dekker, PhD, Jérémy Lévy, DSc: Novartis Pharma AG, Basel, Switzerland; [7]Fabrizio De Benedetti, MD: Bambino Gesù Children's Hospital, Rome, Italy; [8]Helen Lachmann, MD: University College London School of Medicine, London, England.

Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/art.42695).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/art.42695.

Address correspondence via email to Marco Gattorno, MD, at marcogattorno@gaslini.org, or Fabrizio De Benedetti, MD, at fabrizio.debenedetti@opbg.net.

Submitted for publication January 19, 2023; accepted in revised form September 1, 2023.

management of TRAPS reflected the limitations of standard antiinflammatory treatments in effective long-term management.[9] TNF inhibitors are not recommended as a first-line treatment of TRAPS because of their transient and partial effect.[9] However, anti–IL-1 therapies have been shown to be an effective treatment strategy, highlighting the role of IL-1β in the pathophysiology of the disease.[10,11] Canakinumab, a fully human anti–IL-1β monoclonal antibody, is approved by the European Medicines Agency and US Food and Drink Administration for the treatment of TRAPS.[11–14] The approval was supported by the pivotal phase III CLUSTER trial, which investigated the use of canakinumab in three cohorts of patients with hereditary recurrent fevers (HRFs), including one cohort with TRAPS.[12] In all three cohorts, significantly more patients receiving canakinumab than those receiving placebo reached complete response (the primary endpoint), defined as recovering from the baseline flare within 2 weeks with no additional flares by week 16. For the TRAPS cohort, the proportion of patients with complete responses were 45% versus 8% in the canakinumab and placebo groups, respectively.[12] Here, we report results from epoch 4 of CLUSTER, a 72-week period (weeks 41–113 postbaseline) of open-label treatment designed to study the long-term safety and efficacy of canakinumab in patients with TRAPS.

METHODS

Study design. The CLUSTER trial was a phase III study evaluating the efficacy and safety of canakinumab in patients with HRFs, including colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, or TRAPS. The study design has previously been described[12] and is illustrated in Supplementary Figure 1. In brief, the study included three cohorts, one per condition, and was split into four epochs: a screening period of up to 12 weeks (epoch 1; weeks −12 to 0); a 16-week, randomized, double-anonymized, placebo-controlled period (epoch 2; weeks 0 to 16); a 24-week, randomized, open-label withdrawal period (epoch 3; weeks 17 to 40); and a 72-week, open-label treatment period (epoch 4; weeks 41 to 113). To fulfill requests by health authorities and provide access to canakinumab treatment, 18 patients with TRAPS who had previously participated in a phase II study (NCT01242813) or the subsequent patient access program joined the CLUSTER trial at the start of epoch 3 (rollover cohort). This article reports the results of epoch 4 among the cohort of patients with TRAPS.

At the start of epoch 2, patients were randomized to canakinumab 150 mg (or 2 mg/kg in patients ≤40 kg) every 4 weeks (q4w) or placebo. If a flare occurred, up-titration up to 300 mg (or 4 mg/kg) q4w was permitted, or if in the placebo group, patients could begin treatment with canakinumab. Patients receiving canakinumab at the end of epoch 2 entered epoch 3. All patients randomized to placebo at baseline who completed epoch 2 without re-flare were considered placebo responders. To avoid exposure to canakinumab, which may not have been justified given their clinical status, these patients were withdrawn from study treatment.

Nonresponders received open-label canakinumab 150 mg (or 2 mg/kg) or 300 mg (or 4 mg/kg) every 8 weeks (q8w), and responders were re-randomized to anonymized canakinumab 150 mg or placebo q8w. For re-randomized participants, up-titration to 150 mg q4w (or switch to canakinumab 150 mg q8w in the placebo group) was permitted if flares occurred. Patients continuing open-label canakinumab treatment in epoch 3 continued to receive the dose they were receiving at the end of epoch 2 (150 mg or 300 mg) but were switched to a q8w dosing interval, with the option to revert to q4w if a flare occurred. The rollover patients from the phase II study, who joined the CLUSTER study at epoch 3, continued to receive their prior dose of canakinumab (150 mg or 300 mg) with a q8w dosing interval.

Patients who completed epoch 3 on placebo entered epoch 4 and attended scheduled visits but did not receive canakinumab unless they experienced a flare, in which case they started open-label canakinumab 150 mg q8w. All other patients entering epoch 4 continued on the same regimen that they were receiving at the end of epoch 3. If flares occurred in epoch 4, open-label up-titration from 150 mg q8w to 150 mg q4w to 300 mg q4w was permitted. Patients entering epoch 4 on 300 mg q8w were permitted to up-titrate to 300 mg q4w if flares occurred. Down-titration was not allowed during epoch 4, and all treatments were given open label. Throughout the study, patients with a body weight of ≤40 kg received weight-based dosing of canakinumab (2 mg/kg and 4 mg/kg instead of 150 mg and 300 mg, respectively).

A full investigator list can be found in Supplementary Table 1; the study was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Independent Ethics Committee or Institutional Review Board at each center (Supplementary Table 2). This publication was written in accordance with Good Publications Practice (2022) guidelines.[15] All patients or their guardians provided written informed consent before any trial-related procedures.

Objectives. The primary objective of CLUSTER was to evaluate the efficacy of canakinumab 150 mg q4w versus placebo for the achievement of a clinically meaningful reduction in disease activity during epoch 2, defined as resolution of the baseline flare by day 15 and no new flares over the 16-week period. This primary endpoint was met for the three cohorts of patients, and results have been previously reported.[12]

Objectives specific to epoch 4 (weeks 41–113 postbaseline) included evaluation of long-term safety and tolerability as a secondary objective of CLUSTER. Long-term efficacy was evaluated in epoch 4 in terms of PGA scores, number of flares, and serum C-reactive protein (CRP) and serum amyloid A protein (SAA) levels (all exploratory objectives).

Patients and patient and public involvement. Full eligibility criteria for the overall CLUSTER study have been reported previously.[12] For the TRAPS cohort, patients were required to

have a clinical diagnosis of TRAPS with chronic or recurrent disease activity (with a history of >6 flares/year), a mutation of the *TNFRSF1A* gene, and no active flares to enter epoch 1. During epoch 1, patients with an active flare (physician global assessment [PGA] ≥2 and CRP >10 mg/L) were eligible for randomization at the start of epoch 2.

Patients with TRAPS who entered the CLUSTER study at the start of epoch 3 (n = 18), rolling over from the phase II study, were not required to have an active flare at the time of study entry. These patients entered the study at day 113. For patients who were part of the CLUSTER study from the beginning, baseline is defined as day 1 of the study, ie, the start of epoch 2; for patients from the rollover cohort, who entered the study at the beginning of epoch 3, baseline is defined as the start of epoch 3. Labeling of scheduled visits for all patients is based on the scheduled visits of patients who were in the study from the beginning. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of the research.

Assessments. During epoch 4, efficacy and safety assessments were performed q8w. PGA was evaluated by investigators as previously reported. New disease flares were defined as a PGA score ≥2 with a CRP ≥30 mg/L. CRP and SAA were measured at the local and central laboratories, respectively. Safety assessments included frequency and severity of adverse events (AEs).

Statistical analysis. All analyses of safety and efficacy endpoints used the safety analysis set, which consisted of all patients with TRAPS who received study treatment during epoch 4. Data were analyzed among the patient groups based on the cumulative dose of canakinumab received adjusted per kilogram of body weight (<36 mg/kg or ≥36 mg/kg). This approach was adopted because it was expected that some patients would have a flare during the 72-week treatment period and therefore receive up-titration of the dose. The 36 mg/kg cutoff was selected because, in theory, it meant that the cumulative low-dose group (<36 mg/kg) included patients starting epoch 4 with intermediate dose regimens (ie, 150 mg q4w or 300 mg q8w), regardless of whether they subsequently received up-titration. The overall assumption with this cutoff was that half of the population would be in one category, with up-titrated patients moving towards the ≥36 mg/kg dosing group. The relative proportion of responders to canakinumab versus placebo was assessed using a Fisher's exact test for association. Median values were compared using the Kruskal–Wallis test. None of the *P* values were corrected for multiple testing; *P* values are therefore nominal and need to be interpreted accordingly.

RESULTS

Patient disposition and baseline characteristics. Of the 60 patients who entered epoch 3 of the CLUSTER study

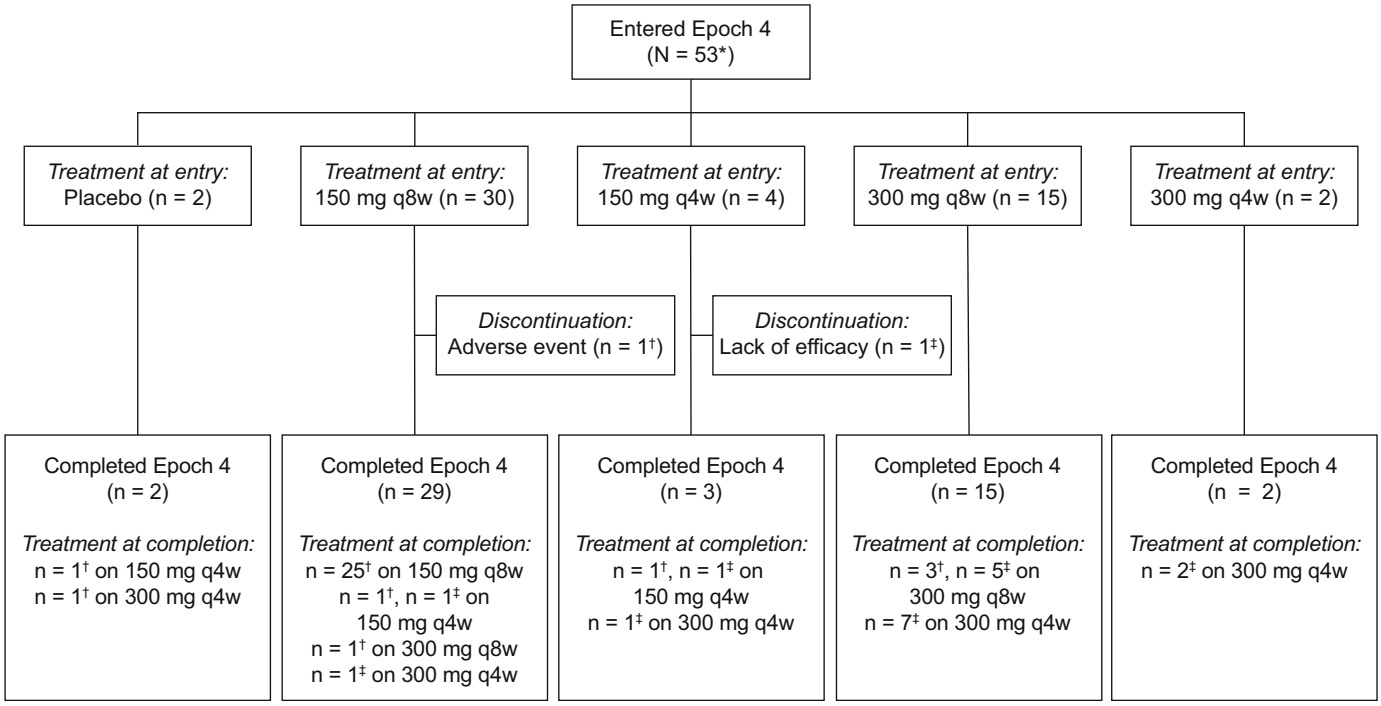


Figure 1. Patient flow diagram showing treatment regimens at the beginning and end of epoch 4 for patients with TRAPS. * Thirty-seven patients who started the study in epoch 2 and 16 patients from the rollover cohort who joined the study at the start of epoch 3. Patients ≤40 kg could receive 2 mg/kg or 4 mg/kg; †cumulative dose <36 mg/kg; ‡cumulative dose ≥36 mg/kg. N, total number of patients; n, number of patients; q4w, every 4 weeks; q8w, every 8 weeks; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

(42 from epoch 2 and 18 from the rollover cohort), 53 entered epoch 4 (37 patients who started the study in epoch 2 and 16 patients from the rollover cohort who joined the study at the start of epoch 3) and 51 completed it. Seven patients from epoch 3 did not enter epoch 4; two were discontinued because of AEs (one case of neutropenia, per common terminology criteria grading, and one because of a reduction in glomerular filtration rate), two because of a lack of efficacy, one per patient/guardian decision, one per physician decision, and one because the patient initiated a prohibited medication.

During the 72 weeks of epoch 4, 34 patients (64.2%) received a cumulative low dose of canakinumab <36 mg/kg, with a median dose of 21.7 mg/kg, and 19 (35.8%) received a cumulative high dose ≥36 mg/kg, with a median dose of 50.3 mg/kg. Of the patients in the <36 mg/kg group, 30 (88.2%) started epoch 4 on either the lowest dose of canakinumab (150 mg q8w in patients >40 kg or 2 mg/kg q8w in patients ≤40 kg) or without treatment, with one patient (2.9%) starting on 150 mg q4w and three patients (8.8%) starting on 300 mg (or 4 mg/kg in patients ≤40 kg) q8w. In the ≥36 mg/kg group, 17 patients (89.5%) started epoch 4 on ≥150 mg q4w of canakinumab (12 patients [63.2%] on 300 mg q8w, 2 [10.5%] on 300 mg q4w, and 3 [15.8%] on 150 mg q4w), whereas 2 patients (10.5%) started on 150 mg q8w. Two patients (3.8%) discontinued treatment; one patient in the <36 mg/kg group discontinued because of an AE (septic shock) and one patient in the ≥36 mg/kg group owing to lack of efficacy (the patient was already receiving the maximum dose and could not undergo up-titration; Figure 1).

Demographics and disease characteristics at baseline are presented in Table 1. Most patients enrolled in epoch 4 were aged ≥12 to <18 years (n = 10, 18.9%) or ≥18 years (n = 30; 56.6%), with a median age of 21.0 years (Table 1). The majority of patients had a body weight of >40 kg (69.8%). Forty patients (75.5%) presented with a pathogenic mutation, whereas only 12 patients (22.6%) presented with variants of unknown significance (VUSs), mainly R92Q (also known as R121Q). Most patients with pathogenic mutations were ≥18 years (27 of 40; 67.5%). Most patients with pathogenic mutations weighed >40 kg (32 of 40; 80.0%) and therefore did not require weight-adjusted doses, whereas only 4 of 12 patients (33.3%) with VUSs weighed >40 kg and did not receive doses adjusted by weight. At baseline, patients had experienced a median of 9.0 flares per year, and most had mild or moderate disease activity. Patients in the cumulative high-dose group (≥36 mg/kg) were younger than those in the low-dose group (<36 mg/kg) and had a lower median body weight, and a lower proportion had pathogenic mutations; however, these baseline characteristics did not appear to significantly influence whether a patient would require higher doses of canakinumab (Supplementary Table 3).

Table 1. Baseline demographic and disease characteristics (safety set)*

Characteristics	Patients (N = 53)
Age	
Median age, years (Q1–Q3)	21.0 (12.0–44.0)
<12 years, n (%)	13 (24.5)
≥12 to <18 years, n (%)	10 (18.9)
≥18 years, n (%)	30 (56.6)
Female, n (%)	26 (49.1)
Race, n (%)	
Caucasian	45 (84.9)
Asian	6 (11.3)
Other	2 (3.8)
Weight	
Median, kg (Q1–Q3)	58.4 (34.7–77.0)
≤40 kg, n (%)	16 (30.2)
>40 kg, n (%)	37 (69.8)
Median BMI at screening, kg/m^2 (Q1–Q3)	21.8 (18.0–26.5)
Median duration of disease, years (Q1–Q3)	11.8 (6.3–31.8)
Median number of flares per year (Q1–Q3)	9.0 (6.0–12.0)
CRP[a] (mg/L), median (Q1–Q3)	69.0 (10.0–163.0)
SAA (mg/L), median (Q1–Q3)	243.0 (13.0–1,712.0)
PGA score (disease activity), n (%)	
0 (None)	11 (20.8)
1 (Minimal)	2 (3.8)
2 (Mild)	17 (32.1)
3 (Moderate)	19 (35.8)
4 (Severe)	4 (7.5)
Type of *TNFRSF1A* mutation, n (%)	
Pathogenic	40 (75.5)
VUS	12 (22.6)
R92Q	9 (17.0)
Other	3 (5.7)
Missing	1 (1.9)

* For patients who were part of the CLUSTER study from the beginning, baseline is defined as day 1 of the study, ie, the start of epoch 2; for patients from the rollover cohort, who entered the study at the beginning of epoch 3, baseline is defined as the start of epoch 3.
BMI, body mass index; CRP, C-reactive protein; N, total number of patients; n, number of patients; PGA, physician global assessment; SAA, serum amyloid A; VUS, variant of unknown significance.
[a] A flare was defined as a CRP level of >10 mg/L.

Control of disease activity. Throughout epoch 4, the majority of patients had PGA scores indicative of no or minimal disease activity (Figure 2). At the end of epoch 4, 94.1% of patients (n = 32) in the <36 mg/kg group and 94.7% of patients (n = 18) in the ≥36 mg/kg group had no or minimal disease activity. Moderate or severe disease activity was not reported in any patient either at the beginning (week 41) or end of epoch 4 (week 113).

Complete clinical response was defined as the absence of flares during epoch 4 and was reached by 37 patients (69.8%), whereas 13 patients (24.5%) had one single flare. More patients had no flares in the canakinumab <36 mg/kg group (n = 28; 82.4%) than in the ≥36 mg/kg group (n = 9; 47.4%), and fewer patients in the <36 mg/kg group had one flare (n = 5; 14.7%) versus the ≥36 mg/kg group (n = 8; 42.1%). Of the remaining patients, two (3.8%) had two flares (one patient in each dose group), and one (1.9%) had three flares (≥36 mg/kg group). The mean incidence of flare during epoch 4 was 0.15 per patient-year in the <36 mg/kg group and 0.49 in the ≥36 mg/kg group. According to genotype, the percentages of patients experiencing

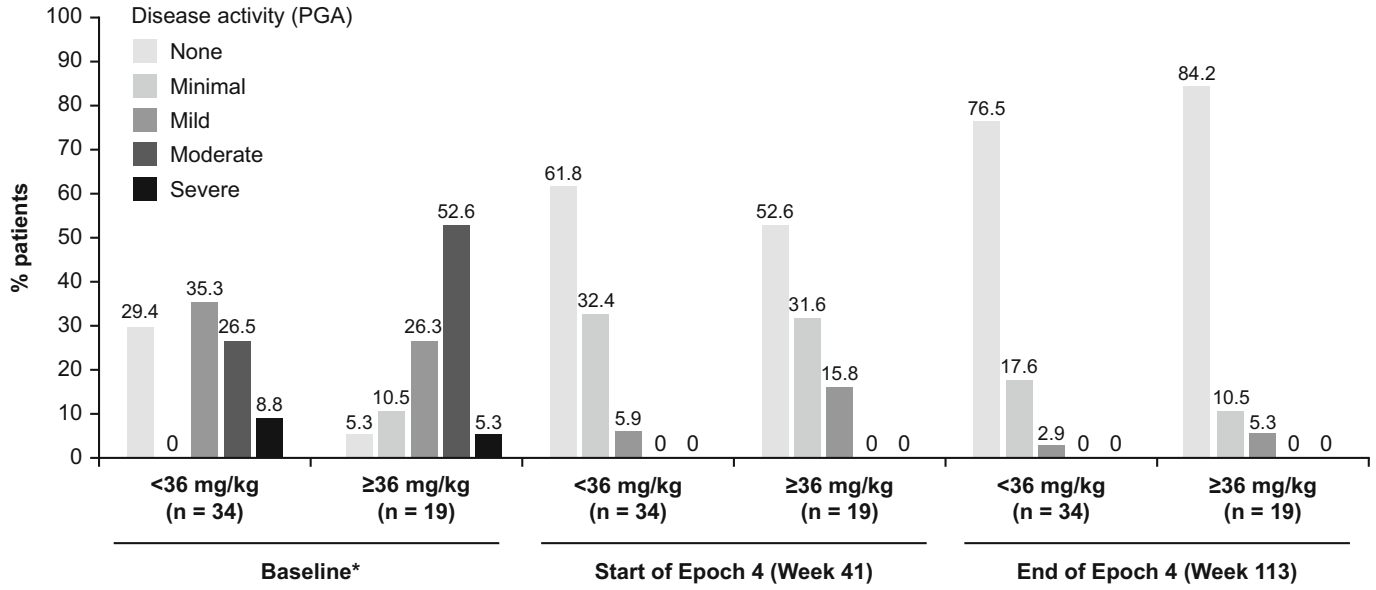


Figure 2. Disease activity as measured by PGA over time. Percentages of patients were calculated using the total number of patients per group as a denominator, ie, <36 mg/kg (N = 34) and ≥36 mg/kg (N = 19). * For patients who were part of the CLUSTER study from the beginning, baseline is defined as day 1 of the study, ie, the start of epoch 2; for patients from the rollover cohort, who entered the study at the beginning of epoch 3, baseline is defined as the start of epoch 3. PGA, physician global assessment.

a flare in epoch 4 and carrying pathogenic mutations versus VUSs were 25% and 50%, respectively (Table 2).

The potential influence of patient baseline characteristics on the long-term response to canakinumab is summarized in Table 2. Although differences were nonsignificant, patients with higher body weight seemed to respond better to canakinumab, and there were trends favoring older patients and those with pathogenic mutations. As mentioned previously, these three parameters were associated in this population; ie, patients with higher body weight were also older and had a higher prevalence of pathogenic mutations. No other baseline characteristics analyzed appeared to affect response to canakinumab.

Table 2. Baseline predictors of response during epoch 4 (safety set)*

Characteristics	No flare during epoch 4 (complete clinical response), N = 37	Flare during epoch 4,[a] N = 16	*P* value[b]
Age			
Median age, years (Q1–Q3)	24.0 (14.0–46.0)	16.0 (5.0–24.5)	0.051
<12 years, n (%)	6 (46.2)	7 (53.8)	
≥12 to <18 years, n (%)	9 (90.0)	1 (10.0)	
≥18 years, n (%)	22 (73.3)	8 (26.7)	0.087
Weight			
Median, kg (Q1–Q3)	64.4 (47.0–79.6)	37.0 (21.0–63.2)	0.021
≤40 kg, n (%)	8 (50.0)	8 (50.0)	
>40 kg, n (%)	29 (78.4)	8 (21.6)	0.054
Median duration of disease, years (Q1–Q3)	11.8 (6.6–34.4)	12.5 (5.2–21.4)	0.488
CRP (mg/L), median (Q1–Q3)	73.5 (14.0–192.5)	53.5 (5.9–151.3)	0.269
SAA (mg/L), median (Q1–Q3)	116 (19.0–1,712.0)	600 (12.0–1,699.5)	0.977
Type of *TNFRSF1A* mutation, n (%)			
Pathogenic	30 (75.0)	10 (25.0)	0.153
VUS	6 (50.0)	6 (50.0)	
Missing	1 (100.0)	0	
Prior use of anakinra, n (%)	10 (83.3)	2 (16.7)	0.307

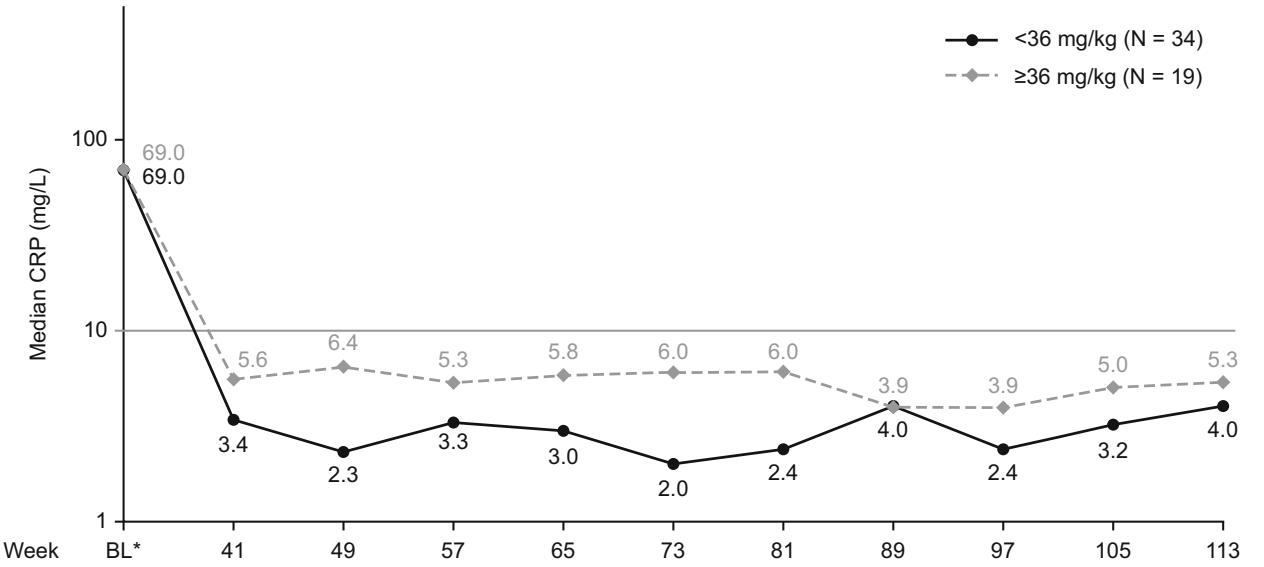
* Percentages were calculated using the number of patients in each category as the denominator (eg, for patients <12 years: six responders in a group of 13 patients in this age category, ie, 46.2%). For patients who were part of the CLUSTER study from the beginning, baseline is defined as day 1 of the study, ie, the start of epoch 2; for patients from the rollover cohort, who entered the study at the beginning of epoch 3, baseline is defined as the start of epoch 3. CRP, C-reactive protein, n, number of patients; SAA, serum amyloid A; VUS, variant of unknown significance.

[a] 13 patients (24.5%) had one single flare; two patients (3.8%) had two flares; and one patient (1.9%) had three flares.

[b] Occurrences are compared using Fisher's exact test for association. Median values were compared using the Kruskal–Wallis test. None of the *P* values were corrected for multiple testing; *P* values are therefore nominal and need to be interpreted accordingly.

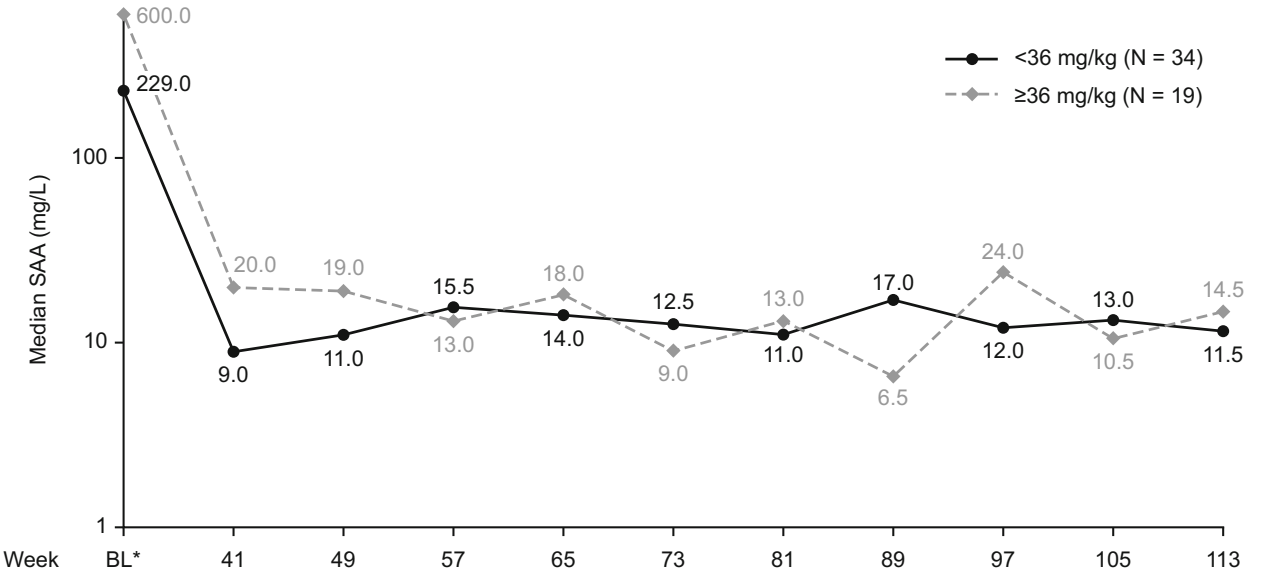
To achieve good disease control, the dose of canakinumab could be intensified, as explained in the Methods section. Two patients who started epoch 4 with no treatment went on to experience flares and required the initiation of canakinumab; most patients on canakinumab q8w at the start of epoch 4 did not require dose intensification (Figure 1). Overall, half of the patients

A Median CRP concentrations



Week	BL*	41	49	57	65	73	81	89	97	105	113
<36 mg/kg Q1–Q3	10.0–163.0	1.5–6.0	1.4–6.0	1.3–6.0	1.2–6.0	1.0–5.8	0.7–6.8	1.5–10.0	0.9–8.8	1.2–5.8	1.0–10.0
≥36 mg/kg Q1–Q3	7.0–181.8	2.0–22.0	4.0–13.2	2.4–6.6	4.0–10.0	2.8–10.7	2.0–8.6	1.6–6.1	1.2–8.8	2.4–9.2	2.0–11.4

B Median SAA concentrations



Week	BL*	41	49	57	65	73	81	89	97	105	113
<36 mg/kg Q1–Q3	11.0–2056.0	5.0–24.0	5.0–29.0	5.0–24.0	8.0–27.0	4.0–28.0	7.0–22.0	7.0–57.0	8.0–37.0	5.0–22.0	4.0–26.0
≥36 mg/kg Q1–Q3	33.0–1712.0	6.0–61.0	4.0–86.0	4.0–50.0	8.0–25.0	5.0–24.0	4.0–34.0	4.0–17.0	5.5–52.5	5.0–24.0	7.0–39.0

Figure 3. CRP and SAA levels in patients with TRAPS over time. (A) The Y-axis is presented using a logarithmic scale, with the upper limit of normal value (10 mg/L) indicated by a solid gray line. The table under the graphic presents the interquartile range (Q1 to Q3) for each time point. The number of patients with data available for each time point (n) ranged from 31 to 34 (<36 mg/kg group) and from 17 to 19 (≥36 mg/kg group). Of note, high baseline values were expected because active disease was an eligibility criterion to enter the study. (B) The table under the graphic presents the interquartile range (Q1 to Q3) for each time point. The number of patients with data available for each time point (n) ranged from 30 to 34 (<36 mg/kg group) and from 16 to 19 (≥36 mg/kg group). BL, baseline; CRP, C-reactive protein; SAA, serum amyloid A.

had good control of the disease with the lower dose of 150 mg q8w, and only 13 patients (24.5%) were receiving the highest dose (300 mg q4w) at the end of epoch 4.

CRP and SAA concentrations. Patients enrolled in the study had high CRP levels at baseline, which decreased with canakinumab treatment during epoch 2. At the start of epoch 4, median CRP levels were 3.4 mg/L and 5.6 mg/L in the canakinumab <36 mg/kg and ≥36 mg/kg groups, respectively, and remained stable throughout the following 72 weeks (Figure 3A). Median CRP levels were typically slightly higher in the ≥36 mg/kg group versus the <36 mg/kg group but remained below 6.4 mg/L and therefore well under the upper limit of normal (10 mg/L) throughout epoch 4 (weeks 41–113). At all time points, the large majority of patients in both dose groups had normal CRP levels. It should be noted that 15 patients (28.3%) had CRP ≤10 mg/L at baseline. These patients were part of the rollover cohort from the phase II study and entered the study at the start of epoch 3; these patients did not need to have a flare at baseline to join the study.

SAA levels were reduced from baseline with canakinumab treatment during epoch 2. At the start of epoch 4, median SAA levels were 9.0 mg/L and 20.0 mg/L in the <36 mg/kg and ≥36 mg/kg groups, respectively, and remained remarkably stable throughout epoch 4 (weeks 41–113), without notable differences between groups (Figure 3B).

Safety. Among the 53 patients enrolled in epoch 4, 50 had a duration of exposure to canakinumab of >68 weeks (94.3%). Median duration of exposure across all patients in epoch 4 was 72.1 weeks.

AEs were reported by all patients in epoch 4. The exposure-adjusted event rate per 100 patient-days was lower in the <36 mg/kg group (1.36) than the ≥36 mg/kg group (2.02) (Table 3). The most common individual AEs were pyrexia and viral upper respiratory tract infections, both of which occurred in more patients in the ≥36 mg/kg group than in the <36 mg/kg group. Many of the commonly reported AEs related to known disease symptoms.

Most AEs were mild or moderate in severity (97.7% of events in the total patient population). Serious AEs (SAEs) were reported in eight patients (15.1%), with a similar incidence in the two dose groups. Two serious infections occurred, both in the <36 mg/kg group (one case of septic shock, leading to treatment discontinuation; one case of vulval abscess, which the patient recovered from without treatment discontinuation). One patient had neutropenia of moderate severity, which was not considered to be related to study treatment and resolved without dose adjustment. In the overall population, grade 1 decreases in neutrophil count occurred in five patients (9.4%), grade 2 decreases occurred in three patients (5.7%), and grade 3 decreases occurred in one patient (1.9%); there were no grade 4 decreases. There were no opportunistic infections or deaths reported.

DISCUSSION

Data previously reported from the CLUSTER study have shown that the anti–IL-1β monoclonal antibody canakinumab is effective at controlling and preventing flares in patients with TRAPS through 40 weeks of treatment.[12] Here, we report longer-term data from this study, demonstrating that continuous

Table 3. Exposure-adjusted incidence of AEs per 100 patient-days and total number of AEs in epoch 4 (safety set)*

	Cumulative dose adjusted per kg of body weight, <36 mg/kg (N = 34); total exposure: 17,071 patient-days[a]; event rate (n)[b]	Cumulative dose adjusted per kg of body weight, ≥36 mg/kg (N = 19); total exposure: 9,684 patient-days[a]; event rate (n)[b]	All patients (N = 53); total exposure: 26,755 patient-days[a]; event rate (n)[b]
Any AE	1.36 (232)	2.02 (196)	1.60 (428)
Most common AEs[c]			
Pyrexia	0.07 (12)	0.31 (30)	0.16 (42)
Viral URTI	0.07 (12)	0.23 (22)	0.13 (34)
Headache	0.08 (13)	0.11 (11)	0.09 (24)
Abdominal pain	0.05 (9)	0.04 (4)	0.05 (13)
Injection site reaction	0.07 (12)	0.01 (1)	0.05 (13)
Nonviral URTI	0.04 (7)	0.06 (6)	0.05 (13)
Cough	0.04 (7)	0.05 (5)	0.04 (12)
Diarrhea	0.04 (6)	0.06 (6)	0.04 (12)
Arthralgia	0.03 (5)	0.06 (6)	0.04 (11)
Rhinitis	0.04 (7)	0.03 (3)	0.04 (10)
SAEs	0.06 (10)	0.05 (5)	0.06 (15)
Serious infections	0.01 (2)	0	0.01 (2)
AEs leading to discontinuation	0.01 (1)	0	0 (1)
Deaths	0	0	0

* AE, adverse event; n, number of patients; SAE, serious AE; URTI, upper respiratory tract infection.
[a] Exposure to canakinumab in each group, in patient-days.
[b] Incidence rate per 100 patient-days and total number of events in the 72-week period.
[c] AEs with ≥10 total events across all patients in the safety set.

treatment with canakinumab provides sustained disease control through an additional 72 weeks of therapy (epoch 4 of the CLUSTER study). Indeed, more than two-thirds of patients experienced no flares during this treatment period, and 94.3% of patients experienced either no flares or only a single flare.

To achieve disease control, the dose of canakinumab could be intensified in individuals during this open-label 72-week treatment period. Although not statistically significant, those patients who received a higher cumulative dose of canakinumab (that is, those receiving a cumulative dose of ≥36 mg/kg when adjusted for body weight) tended to be younger and have a lower body weight than those who received a lower cumulative dose (<36 mg/kg), suggesting a potential need for higher doses in children. The relative proportion of patients with pathogenic mutations versus VUSs was greater in the lower cumulative dose group (82.4% vs 14.7%) compared with the higher cumulative dose group (63.2% vs 36.8%). This finding is in line with real-world data, showing a greater efficacy of anti–IL-1 treatments in patients carrying *TNFSRF1A* pathogenic mutations rather than VUSs.[3] Although firm conclusions cannot be made, it may be useful to take these findings into consideration when choosing or modifying individual canakinumab dosing regimens in patients with TRAPS in clinical practice. Regardless, the data presented here demonstrate that the level of disease control achieved in patients with TRAPS requiring high doses of canakinumab is similar to that achieved in patients needing lower doses. Similar findings with canakinumab have been reported in patients with other HRFs.[12]

The safety profile of long-term canakinumab treatment observed here in epoch 4 of the CLUSTER study was consistent with previous reports,[12] with no new or unexpected safety findings. In addition, no association was observed between increased cumulative dose of canakinumab and the occurrence of serious infections or SAEs.

At present, treatment regimens for patients with TRAPS are mainly driven by individual patients' clinical presentation and inflammation markers, which, in this study, were shown to be largely safe and effective methods to achieve disease control. As mentioned, up-titration of canakinumab was permitted in patients who experienced a disease flare during the CLUSTER study (defined as a PGA score ≥2 with a CRP ≥30 mg/L); in the real-world setting, the need and duration of dose escalation is something that should be carefully considered, particularly in patients exhibiting persistent evidence of disease activity, such as frequent disease flares or persistent elevation of acute phase reactants.

On the other hand, the present study also includes the possibility of down-titration in patients with persistent control of disease activity. In fact, 25 out of 53 patients with TRAPS (47.2%) completed epoch 4 using the lower dose of 150 mg q8w. Comparatively, similar studies reported that the same dose was achieved by 23 out of 60 patients with colchicine-resistant familial Mediterranean fever (38.3%) and 13 out of 66 patients with mevalonate kinase deficiency (19.7%).[16,17] These findings suggest a difference in the possibility of reducing the dosage regimen among these three HRFs.

Long-term observational studies in a real-world setting will investigate the best maintenance dose regimen in patients with TRAPS. Moreover, further research could seek to investigate biomarkers able to determine optimal treatment regimens with limited up-titration or adjustment required.

The limitations of this long-term study include the open-label administration of canakinumab, the lack of a control group, and the limited number of patients. Nonetheless, the results of this study demonstrate that use of canakinumab can result in sustained disease control in patients with TRAPS and confirm canakinumab as a potential long-term treatment option for these patients.

ACKNOWLEDGMENTS

The authors thank the patients, study site staff, and additional investigators for their participation in the study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Gattorno and De Benedetti had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gattorno, Dekker, De Benedetti, Lachmann.

Acquisition of data. Gattorno, Obici, Calvo Penadés, Kallinich, Benseler, De Benedetti, Lachmann.

Analysis and interpretation of data. Gattorno, Obici, Calvo Penadés, Kallinich, Benseler, Dekker, Lévy, De Benedetti, Lachmann.

ROLE OF THE STUDY SPONSOR

The study was designed by the authors and Novartis Pharma AG. Novartis had no role in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Novartis. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Samuel McCracken, Peter Birch, Christopher Strutynskyj-Stannard, and Eleanor Thomas of Ashfield MedComms, An Inizio Company.

REFERENCES

1. Kontzias A, Zarabi SK, Calabrese C, et al. Somatic mosaicism in adult-onset TNF receptor-associated periodic syndrome (TRAPS). Mol Genet Genomic Med 2019;7:e791.
2. De Jesus AA, Goldbach-Mansky R. Genetically defined autoinflammatory diseases [review]. Oral Dis 2016;22:591–604.
3. Papa R, Lane T, Minden K, et al; Pediatric Rheumatology International Trials Organization (PRINTO), the EUROTRAPS, and the Eurofever Project. INSAID variant classification and Eurofever criteria guide optimal treatment strategy in patients with TRAPS: data from the Eurofever Registry. J Allergy Clin Immunol Pract 2021;9:783–791.e4.
4. Lachmann HJ, Papa R, Gerhold K, et al; Paediatric Rheumatology International Trials Organisation (PRINTO), the EUROTRAPS and the Eurofever Project. The phenotype of TNF receptor-associated

autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. Ann Rheum Dis 2014;73:2160–2167.

5. Pettersson T, Kantonen J, Matikainen S, et al. Setting up TRAPS [review]. Ann Med 2012;44:109–118.
6. Simon A, Park H, Maddipati R, et al. Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. Proc Natl Acad Sci U S A 2010;107:9801–9806.
7. Jarosz-Griffiths HH, Holbrook J, Lara-Reyna S, et al. TNF receptor signalling in autoinflammatory diseases [review]. Int Immunol 2019; 31:639–648.
8. Ter Haar N, Lachmann H, Özen S, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Eurofever/Eurotraps Projects. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review [review]. Ann Rheum Dis 2013;72:678–685.
9. Ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases [review]. Ann Rheum Dis 2015;74:1636–1644.
10. Gattorno M, Pelagatti MA, Meini A, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008;58:1516–1520.
11. Gattorno M, Obici L, Cattalini M, et al. Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. Ann Rheum Dis 2017;76:173–178.
12. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med 2018;378:1908–1919.
13. European Medicines Agency. ILARIS (canakinumab). Summary of Product Characteristics (SmPC). Accessed August 16, 2022. https://www.ema.europa.eu/en/documents/product-information/ilaris-epar-product-information_en.pdf
14. Food and Drink Administration. ILARIS (canakinumab). Highlights of Prescribing Information. Accessed August 16, 2022. https://www.novartis.com/us-en/sites/novartis_us/files/ilaris.pdf
15. DeTora LM, Toroser D, Sykes A, et al. Good Publication Practice (GPP) guidelines for company-sponsored biomedical research: 2022 update. Ann Intern Med 2022;175:1298–1304.
16. Özen S, Ben-Cherit E, Foeldvari I, et al. Long-term efficacy and safety of canakinumab in patients with colchicine-resistant familial Mediterranean fever: results from the randomised phase III CLUSTER trial. Ann Rheum Dis 2020;79:1362–1369.
17. Jeyaratnam J, Simon A, Calvo I, et al. Long-term efficacy and safety of canakinumab in patients with mevalonate kinase deficiency: results from the randomised Phase 3 CLUSTER trial. Rheumatology (Oxford) 2022;61:2088–2094.