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ORIGINAL RESEARCH

Long-term safety and effectiveness of canakinumab in patients with monogenic autoinflammatory diseases: results from the interim analysis of the RELIANCE registry

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ABSTRACT

Objective Interim analysis of the RELIANCE registry, an on-going, non-interventional, open-label, multicentre, prospective study evaluating the long-term safety, dosing regimens and effectiveness of canakinumab in patients with cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumour-necrosis factor receptor-associated periodic syndrome (TRAPS) or mevalonate-kinase deficiency (MKD)/hyperimmunoglobulin-D syndrome (HIDS).

Methods From September 2017 for patients with CAPS, and June 2018 for patients with FMF, TRAPS or MKD/HIDS, the registry enrolled paediatric (aged ≥2 years) and adult patients (aged ≥18 years) receiving canakinumab as part of their routine medical care. Safety, canakinumab dose, disease activity and quality of life outcome measures were evaluated at baseline and every 6 months until end of study visit.

Results At the analysis cut-off date (December 2020), 168 patients (91 CAPS, 54 FMF, 16 TRAPS and 7 MKD/HIDS) were enrolled. 85 (50.9%) patients were female and 72 (43.1%) were children (<18 years). The median patient age was 20.0 years (range 2.0–79.0 years). In the CAPS cohort, serious infections and serious adverse drug-reactions were more common in patients receiving higher than the recommended starting dose (SD) of canakinumab. A trend to receive >SD of canakinumab was observed in the pooled population. The majority of patients were reported as having either absent or mild/moderate disease activity (physician's global assessment) from baseline to Month 30, with a stable proportion of patients (~70%) in remission under canakinumab treatment. Patient-reported disease activity (Visual Analogue Scale (VAS), Autoinflammatory Disease Activity Index), fatigue (VAS); markers of inflammation (C-reactive protein, serum amyloid A and erythrocyte sedimentation rate) remained well-controlled throughout.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumour-necrosis factor receptor-associated periodic syndrome (TRAPS) and mevalonate-kinase deficiency (MKD)/hyperimmunoglobulin-D syndrome (HIDS) are a group of monogenic autoinflammatory diseases that share a pathogenesis driven by the pro-inflammatory cytokine interleukin (IL)-1.

⇒ The available clinical trial and real-world data demonstrate that canakinumab, a fully human, anti-IL-1β monoclonal antibody, is an effective and well-tolerated treatment option for these diseases.

WHAT THIS STUDY ADDS

⇒ The results from this interim analysis confirm the long-term safety profile of canakinumab and its ability to effectively control disease activity in the treatment of CAPS, FMF, TRAPS or MKD/HIDS.

⇒ The results also demonstrate the impact of individual dose adjustments on achieving improvement of disease control and health-related quality of life in the real-world setting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As CAPS, FMF, TRAPS and MKD/HIDS are life-long diseases, the results from this study add to the available evidence for the safety and efficacy of long-term use of canakinumab.

⇒ The observed importance of dose adjustments in achieving disease control in this cohort also highlights the value of treat-to-target strategies in optimising treatment algorithms.

Conclusion Data from this analysis confirm the long-term safety and effectiveness of canakinumab for the treatment of CAPS, FMF, TRAPS and MKD/HIDS.

INTRODUCTION

Cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), tumour-necrosis factor receptor-associated periodic syndrome (TRAPS) and mevalonate-kinase deficiency (MKD), also known as hyperimmunoglobulin-D syndrome (HIDS) are a group of monogenic autoinflammatory diseases (AID) that share a pathogenesis driven by the pro-inflammatory cytokine interleukin (IL)-1.[1–3] CAPS are caused by mutations in *NLRP3* and comprise three phenotypes: the mild familial cold autoinflammatory syndrome (FCAS), the moderate Muckle-Wells syndrome (MWS) and the severe neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous articular syndrome (CINCA).[1–3] FMF is the most common and well-characterised AID and is caused by mutations in *MEFV*, whereas TRAPS and MKD/HIDS are rare AID caused by mutations in *TNFRSF1A* and *MVK*, respectively.[2 3] These diseases predominately present in infancy and are often characterised by recurrent episodes of fever that can last several days or weeks.[2 3] If disease activity is not effectively controlled, AID can lead to progression to more severe conditions associated with persistent systemic inflammation, such as joint or neurological damage, growth restriction and amyloid A amyloidosis.[2 4–6] Moreover, frequent fever episodes or persistent inflammation can affect functional capacity and physiological functioning, leading to poor long-term health-related quality of life (HRQoL).[4 7–9]

In some patients with AID, the long-term use of conventional treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, is unable to achieve sustained control of disease activity by suppressing systemic inflammation and is frequently associated with systemic complications.[3 10–12] Moreover, previous studies have reported that although treatment with colchicine, the primary treatment for patients with FMF, is effective in the majority of patients, inadequate response is observed in 5–10%, and 2–5% of patients experience treatment intolerance.[13] The increasing availability of IL-1 inhibitors has addressed an important unmet medical need for effective treatment options for patients with AID.[3] Canakinumab is a fully human, anti-IL-1β monoclonal antibody that selectively binds to IL-1β, blocking its signalling.[14 15] It is approved by the European Medicines Agency and Food and Drug Administration as a biological maintenance therapy in adults and children with CAPS (since 2009) and FMF, TRAPS and MKD/HIDS (since 2017) at a recommended starting dose, with an intensified dose recommended in patients with an inadequate clinical response.[14 16] The pivotal, randomised, controlled phase 3 CLUSTER study demonstrated that canakinumab is an effective and well-tolerated long-term treatment option for achieving rapid and sustained reductions in disease activity, alongside improving HRQoL in patients with FMF (with an insufficient response to colchicine treatment), TRAPS or MKD/HIDS.[1 4 15 17 18]

There are several management recommendations that advocate the use of IL-1 inhibitors in patients with AID.[3 19 20] The Single Hub and Access Point for Paediatric Rheumatology in Europe (SHARE) recommends the use of IL-1β inhibitors to manage all subtypes of CAPS (at any age), TRAPS and MKD/HIDS to terminate inflammatory attacks, limit or prevent severe corticosteroid-related side-effects, control clinical manifestations or to use when previous treatment has failed to sufficiently control disease activity.[20] In addition, the 2016 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of FMF acknowledge that biologics, such as IL-1 inhibitors, should be considered as second-line therapy for patients with FMF who have an insufficient response or are intolerant to colchicine.[19] The German PRO-KIND initiative working group developed the first evidence-based, actionable treat-to-target consensus treatment plans for patients with CAPS, TRAPS and MKD/HIDS, highlighting the importance of tailored dose adjustments in reaching clinical remission using NSAIDs, corticosteroids, anakinra (an IL-1 receptor antagonist) or canakinumab.[21] The four main goals of this treat-to-target approach include: (1) identification of individual strategies in disease activity, estimated risk and anticipated trajectories; (2) selecting validated monitoring instruments; (3) defining treatment targets and intervals; and (4) providing evidence-based therapies and strategies for adjustment.[21]

Treat-to-target strategies require dose adjustments. The use of canakinumab in routine clinical practice is known to vary in dosages and dosing intervals, across different countries and centres.[1 3 20–23] Although some patients with a mild AID phenotype and limited disease activity benefit from standard and lower than standard doses of IL-1 inhibitors,[3 24] higher than the recommended starting dose of canakinumab has shown effectiveness in paediatric patients and in patients with severe phenotypes or specific genotypes of CAPS, FMF, TRAPS and MKD/HIDS.[1 3 20–23] Results from the global multicentre long-term follow-up β-Confident registry of patients with CAPS indicated that patients with more severe phenotypes required increased doses of canakinumab to achieve complete response rates compared with the recommended starting dose administered in controlled trials, demonstrating the importance of a treat-to-target approach in the real-world use of canakinumab.[23]

The available clinical trial data support the safety and efficacy of canakinumab for the treatment of AID.[14 15 17 18] However, given that AID are life-long diseases that can severely impact paediatric and adult patients' quality of life, there is a need for further data supporting the long-term safety and effectiveness of canakinumab in routine clinical practice. In this manuscript, we present
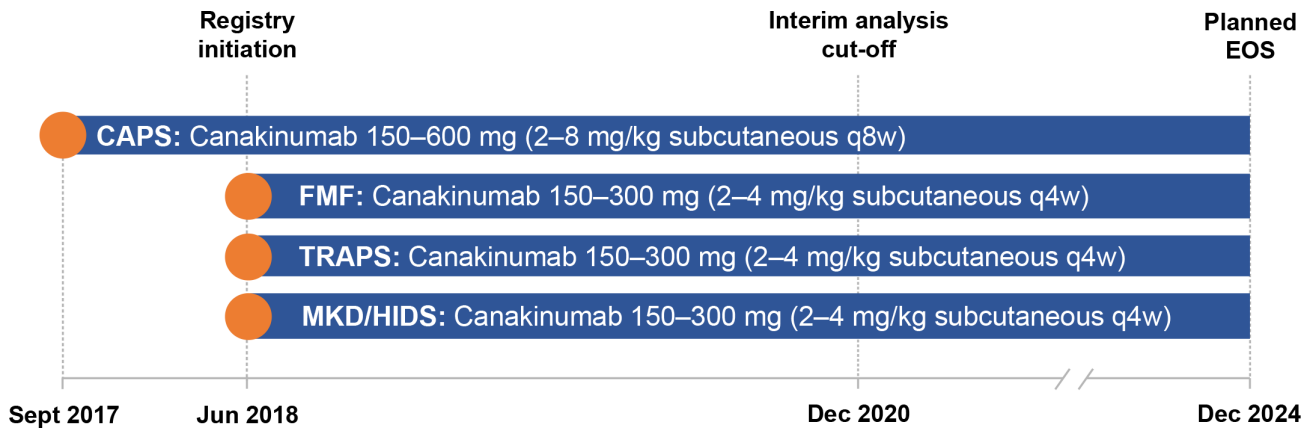
Figure 1 Study design. Treatment decisions were determined by the treating physician according to standard of care and local clinical practice. CAPS, cryopyrin-associated periodic syndromes; EOS, end of study; FMF, familial Mediterranean fever; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; qXw, every X weeks; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

the results from an interim analysis of the RELIANCE registry, a real-world registry investigating the long-term safety and effect on control of disease activity of canakinumab in children and adults with CAPS, FMF, TRAPS and MKD/HIDS in routine clinical practice.

METHODS

Study design and patients

The RELIANCE registry is an on-going, non-interventional, open-label, multicentre, prospective study based in Germany, evaluating the long-term safety outcomes, dosing regimens and effectiveness of canakinumab (control of disease activity).

The registry currently involves 23 study sites across Germany and includes paediatric (aged ≥2 years) and adult patients (aged ≥18 years) receiving canakinumab as part of their routine medical care for clinically confirmed CAPS, FMF, TRAPS or MKD/HIDS. Patients were diagnosed prior to enrolling in the registry and genetic diagnosis was documented in the majority of patients. The registry was initiated in September 2017 for patients with CAPS, and in June 2018 for patients with FMF, TRAPS and MKD/HIDS, with an enrolment period of 4.5 years and a follow-up period of between 1.5 years and 7 years, with study end planned for December 2024 (figure 1). The cut-off date for this interim analysis was 01 December 2020. Treatment and evaluation decisions were determined by the treating physician according to standard of care and local clinical practice, and the choice of therapy was based on the given indication, in line with summary of product characteristics (SmPC) and patient medical need.[14]

The pooled population comprised all patients in the CAPS, FMF, TRAPS and MKD/HIDS patient cohorts. Enrolment included a proportion of patients who had previously participated in the β-Confident registry (referred to as 'β-Confident registry rollovers').[25] Exclusion criteria were: patients receiving canakinumab for autoimmune diseases other than CAPS, FMF, TRAPS

or MKD/HIDS; patients receiving biologics, other than canakinumab, at time of inclusion; patients participating in an interventional clinical trial which would have an impact on routine treatment; any contraindication as per the SmPC.

Dose regimen

The recommended starting dose (SD) of canakinumab was 150 mg or 2 mg per kg of body weight for patients weighing ≤40 kg administered subcutaneously every 8 weeks (q8w) for patients with CAPS, and, every 4 weeks (q4w), for patients with FMF, TRAPS or MKD/HIDS. Less than SD (<SD) was defined as <87.5% of SD and greater than SD (>SD) was defined as >112.5% of SD.

Data collection

Patient characteristics, disease course, non-autoinflammatory-related medical history, canakinumab treatment (dose and interval) and previous and concomitant treatments for each patient cohort, were collected at baseline. Adjustments to canakinumab dosing regimens and safety measures (adverse events (AEs), serious adverse events (SAEs), adverse drug-reactions (ADRs) and serious adverse drug-reactions (SADRs)) were recorded throughout the study. All disease activity and quality of life outcome measures (physician's global assessment of disease activity (PGA), physician's assessment of disease remission (conducted using yes/no answers), inflammatory markers C-reactive protein (CRP), serum amyloid A (SAA) and erythrocyte sedimentation rate (ESR), growth and weight measurements, patient-reported outcomes (assessment of disease activity, fatigue, school/work absence, impacted social life; and autoinflammatory disease activity index diary (AIDAI)) were evaluated at baseline and every 6 months thereafter, until end of study visit or premature discontinuation, in line with the biannual pattern of care most patients received (see online supplemental methods).

Statistical analysis

All patients who had received at least one dose of canakinumab, and for whom at least one follow-up

Table 1 Demographics and baseline characteristics for the pooled population

	All patients (N=168)
Diagnosis, n (%)	
CAPS	91 (54.2)
NOMID/CINCA*	14 (8.3)
FMF	54 (32.1)
TRAPS	16 (9.5)
MKD/HIDS	7 (4.2)
Age, years (N=167)	
Median (range)	20 (2.0–79.0)
Age groups, n (%)	
Children (<18 years)	72 (43.1)
<4 years	2 (1.2)
4 to <12 years	52 (31.1)
12 to <18 years	18 (10.8)
Adults (≥18 years)	95 (56.9)
18 to <65 years	93 (55.7)
≥65 years	2 (1.2)
Sex, n (%) (N=167)	
Female	85 (50.9)
Ethnicity, n (%) (N=167)	
Caucasian	160 (95.8)
Other	7 (4.2)
Diagnosis of mutations, n (%)	
CAPS (n=91)	
NLRP3 mutation	76 (83.5)
FMF (n=54)	
MEFV mutation	53 (98.1)
TRAPS (n=16)	
TNFRSF1A mutation	15 (93.8)
MKD/HIDS (n=7)	
MVK mutation	7 (100.0)
Disease-related symptoms†, n (%)	
Fatigue (N=148)	78 (52.7)
Arthralgia/arthritis (N=148)	46 (31.1)
Headache (N=148)	42 (28.4)
Abdominal pain (N=148)	32 (21.6)
Fever (N=148)	30 (20.3)
Conjunctivitis/uveitis (N=148)	30 (20.3)
Myalgia (N=148)	25 (16.9)
Symptoms induced by cold (N=89)	24 (27.0)
Impairment of hearing (N=89)	22 (24.7)
Symptoms triggered by infection (N=104)	21 (20.2)
Neurological symptoms (N=148)	18 (12.2)

Continued

Table 1 Continued

	All patients (N=168)
PGA of disease activity, n (%) (N=148)	
Severe	7 (4.7)
Mild/moderate	72 (48.6)
Absent	60 (40.5)
Not measured	9 (6.1)
Patient's assessment of disease activity, VAS score (N=163)	
Median (Q1–Q3)	2.0 (0.0–4.0)
CRP, mg/dL (N=154)	
Median (Q1–Q3)	0.2 (0.0–0.5)
SAA, mg/dL (N=137)	
Median (Q1–Q3)	0.5 (0.2–1.3)
ESR, mm/hour (N=122)	
Median (Q1–Q3)	6.0 (4.0–11.0)
Duration of prior canakinumab treatment, years (N=141)	
Median (Q1–Q3)	3.0 (1.0–7.0)

Due to the real-world nature of the RELIANCE registry, execution of standard of care procedures may differ between each centre, resulting in some variability in data collection, in addition to, delayed or missing data yet to collect. Missing values reported within a visit/time point do not refer to the full patient cohort, but to patients who have the visit documented but no data available for the specific outcome measure. The number of patients for each parameter is indicated in the left column if lower than the total number of patients included in this interim analysis.

*Includes patients diagnosed with MWS/NOMID, NOMID/CINCA, NOMID or CINCA.

†Includes patients with severe and mild/moderate symptoms.

CAPS, cryopyrin-associated periodic syndromes; CRP, C-reactive protein; FMF, familial Mediterranean fever; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; MWS, Muckle-Wells syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular; PGA, physician's global assessment; SAA, serum amyloid A; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; VAS, Visual Analogue Scale.

documentation was available, were considered in the evaluation. All variables collected during the registry were evaluated and analysed using descriptive methods. Any confidence intervals (CIs) specified are purely descriptive. Due to the exploratory nature of the evaluation, no alpha adjustment was made for multiple comparisons. Patient discontinuation was not considered during statistical analysis based on the small number of patients in each disease cohort.

For AEs, incidence rates (IRs) per 100 patient-years (PY) are reported based on the included patient population and incidence densities (number of events/sum of observation days) according to Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term for AEs, SAEs, ADRs and SADRs. Poisson regression models were used to obtain AE incidence rates over time between age groups.

RESULTS

Demographic and disease characteristics

The results presented in this manuscript describe the pooled population (unless stated otherwise) and patient percentages are calculated based on the number of patients with available data for each outcome measure. This interim analysis of the RELIANCE registry included data from a total of 168 patients (91 patients with CAPS (8.3% NOMID/CINCA subtypes); 54 patients with FMF; 16 patients with TRAPS and 7 patients with MKD/HIDS) enrolled between September 2017 and December 2020 (table 1).

In total, 85 (50.9%) patients were female and 95 (56.9%) were adults (aged ≥18 years). A total of 54 (32.3%) patients were below the age of 12 and the median age was 20.0 years (range 2.0–79.0 years) (table 1).

Overall, 83.5% patients with CAPS had confirmed *NLRP3* mutations, 98.1% with FMF had known *MEFV* mutations, 93.8% with TRAPS had known *TNFRSF1A* mutations and all patients with MKD/HIDS had known *MVK* mutations (table 1). The respective mutations for each of the disease cohorts are detailed in online supplemental table 1.

At baseline (study inclusion), the proportion of patients rated as having absent, mild/moderate or severe disease activity by PGA, was 40.5%, 48.6% and 4.7%, respectively. Median patients' assessment of disease activity (Visual Analogue Scale (VAS) score) was 2.0 and the median CRP level, SAA level and ESR were 0.2 mg/dL, 0.5 mg/dL and 6.0 mm/hour, respectively. The most common disease-related symptoms were fatigue, arthralgia/arthritis and headache (table 1). Baseline demographics and patient characteristics for individual disease cohorts are detailed in online supplemental table 2.

Patient disposition and canakinumab exposure

The patient disposition for this interim analysis is detailed in online supplemental table 3. In the time between the initiation of the RELIANCE registry and this interim analysis (01 December 2020), seven patients (4.2%, five CAPS and two FMF) discontinued canakinumab. The reasons cited were lack of efficacy (3), loss of efficacy (2), adverse events (1) and disease improvement (1).

Prior to inclusion into the study, median duration of exposure to canakinumab was 3.0 years overall (1.0–7.0 years) (table 1). Median prior exposure to canakinumab was 6.0 years, 2.0 years, 1.0 year and 2.0 years, in the CAPS, FMF, TRAPS and MKD/HIDS cohorts, respectively (online supplemental table 2). In the CAPS cohort, all patients had received prior treatment with canakinumab; 44 (48.9%) patients had received prior canakinumab treatment from previous studies. In total, 40 (93.0%) of these patients were β-Confident registry rollovers.[25] In the FMF cohort, 43 out of 54 (79.6%) patients were pretreated with canakinumab and 34 out of 54 (63.0%) were receiving colchicine as a co-medication (median daily dose 1.43 mg). All 16 patients with TRAPS and all 7 patients with MKD/HIDS had received prior treatment with canakinumab.

Canakinumab dosing

At baseline, the majority of patients were receiving either >SD or SD canakinumab, with this trend also being observed at the interim analysis cut-off (figure 2). In the CAPS cohort (n=80), 2.5% of patients received <SD canakinumab, 48.8% of patients received SD canakinumab and 48.8% of patients received >SD canakinumab (figure 2). Among patients with NOMID/CINCA subtypes (n=14), 8.3% of patients received <SD canakinumab, 50.0% of patients received SD canakinumab and 41.7% of patients received >SD canakinumab. In the FMF cohort (n=47), 4.3% and 76.6% of patients received <SD canakinumab or SD canakinumab, respectively, whereas 0.0% and 73.3% of patients with TRAPS (n=15), and 16.7% and 16.7% of patients with MKD/HIDS (n=6), received <SD canakinumab or SD canakinumab, respectively (figure 2). Of patients with FMF who had no prior canakinumab treatment (n=11), 10.0% of patients received <SD canakinumab and 90.0% of patients received SD canakinumab.

At Month 30, the majority of patients with CAPS (81.8%) received >SD canakinumab. In contrast, the three dosing categories were used in equal proportions in the FMF, TRAPS and MKD/HIDS cohorts at the interim analysis cut-off (figure 2).

When the proportion of patients in each dosing group was averaged over the entire study period, >SD canakinumab was received by ≥60% of paediatric patients with CAPS, TRAPS and MKD/HIDS in the <12 years age group (online supplemental figure 1). In addition, the majority of patients with NOMID/CINCA subtype received >SD canakinumab throughout the study period.

Safety profile of long-term canakinumab

Overall, a total of 489 AEs were reported by 101 (60.1%) patients (IR/100 PY, 173.3) at the interim analysis cut-off (table 2). Infections (32.7%) were the most frequent AEs with an IR/100 PY of 2.2. A total of 13 AEs (12 AEs, 1 SAE) were reported as upper respiratory tract infections, no vertigo and no hypersensitivity reactions were observed. Of 46 registry patients who received at least one vaccine (63 vaccinations were administered in total including 1 live attenuated vaccine), 7 (15.0%) patients reported adverse reactions to vaccination suspected to be study drug-related (non-serious AE). AE data for each individual disease cohort are listed in online supplemental table 4; no SAE were reported in the MKD/HIDS cohort (n=7), although the IR of any non-SAE (p=0.033) and any non-SADR (p=0.004) significantly differed from the IR in all other indications. Incidence rates of the most common AEs in the pooled population are also listed in online supplemental table 5.

A total of 53 SAEs were reported by 22 (13.1%) patients (IR/100 PY, 18.8) including 21 SADRs reported by 9 (5.4%) patients (IR/100 PY, 7.4) (table 2); the most common SAEs and SADRs were pyrexia. The IR/100 PY
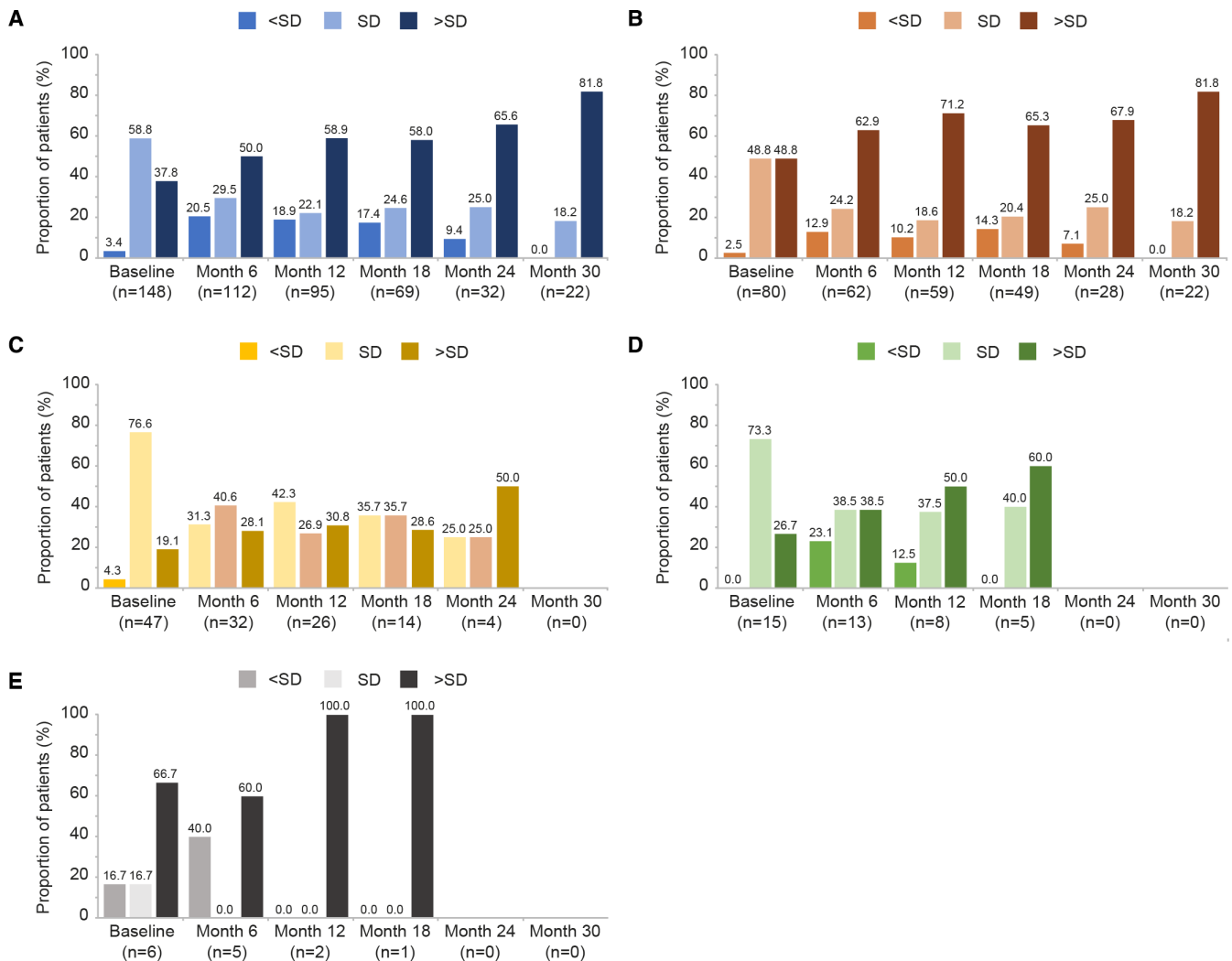
Figure 2 Canakinumab dosing category in (A) pooled population and individual disease cohorts (B) CAPS, (C) FMF, (D) TRAPS, (E) MKD/HIDS. (A) Data were missing for 20, 16, 12, 14, 14, 14 patients at BL, Months 6, 12, 18, 24 and 30, respectively; (B) Data were missing for 11, 9, 7, 9, 8, 8 patients at BL, Months 6, 12, 18, 24 and 30, respectively; (C) Data were missing for 7, 5, 3, 3, 4 patients at BL, Months 6, 12, 18 and 24, respectively; (D) Data were missing for 1, 1, 1, 1 patients at BL, Months 6, 12 and 18, respectively; (E) Data were missing for 1, 1, 1, 1 patients at BL, Months 6, 12 and 18, respectively. The SD of canakinumab was defined as 150 mg (or 2 mg/kg of body weight for patients weighing ≤40 kg) q8w for patients with CAPS, or q4w for patients with FMF, TRAPS or MKD/HIDS. <SD was defined as canakinumab <130 mg q4w for patients with FMF, MKD/HIDS and TRAPS; <130 mg q8w for patients with CAPS; >SD was defined as canakinumab >170 mg q4w for with FMF, MKD/HIDS and TRAPS; >170 mg q8w for patients with CAPS. BL, baseline; CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; qXw, every X weeks; SD, recommended starting dose; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

of SAEs and SADR were higher in the CAPS cohort (20.8 and 10.7, respectively) compared with non-CAPS cohorts (14.7 and 1.1, respectively) (online supplemental figure 2). One fatal outcome occurred (due to COVID-19) in an adult patient with pre-existing renal insufficiency, not related to canakinumab treatment.

A greater number of patients in the >SD canakinumab dosing group experienced SAEs and SADRs than in the <SD canakinumab and SD canakinumab groups although rates were not significantly different (online supplemental table 6). The IR/100 PY of SAE and SADR infections were also highest for patients treated with >SD canakinumab in comparison to the other dosing groups, which was most notable in older children between 12

and 18 years who received >SD canakinumab (IR/100 PY, 9.23/9.23) (online supplemental table 7).

Long-term influence of canakinumab on disease activity

The majority of patients were reported as having either absent or mild/moderate disease activity over time (figure 3). In general, the proportion of patients with severe disease activity decreased, except for patients with CAPS or TRAPS at Month 12 (online supplemental figure 3).

Physicians reported that a stable proportion of patients (~70%) were in disease remission over time in the pooled population (figure 4). Sustained disease remission was observed over time in all CAPS subtypes, with all four

Table 2 AEs, SAEs, SADRs, URTI in the pooled population (all patients, N=168)

Event category	N events (IR*/100 PY)
Any AE	489 (173.3)
Any non-serious AE	436 (154.6)
Any not related non-SAE	221 (78.3)
Any non-serious ADR	215 (76.2)
Any SAE	53 (18.8)
Any not related SAE	32 (11.3)
Any SADR	21 (7.4)
Any URTI	13 (4.6)

*Incidence rate per 100 patient years=number of events × 36 525/ sum of observation days (103 042).
ADR, adverse drug reaction; AEs, adverse events; IR, incidence rate; PY, patient-years; SADRs, serious ADRs; SAEs, serious AEs; URTI, upper respiratory tract infections.

patients with NOMID/CINCA reporting disease remission at Month 30 (online supplemental figure 4). In addition, physicians documented an improvement in disease remission over time in the FMF cohort, particularly in those patients who had not received prior canakinumab therapy. An increased proportion of patients in disease remission was also observed in the MKD/HIDS cohort at Month 12 versus baseline (figure 4).

Patients reported sustained low disease activity, with a median VAS score of 2.0 at baseline and 0.0 at interim analysis cut-off (online supplemental figure 5). Patients with NOMID/CINCA, the severe CAPS-phenotype, reported improved VAS scores of 1.0 at baseline to 0.0 at Month 30 (online supplemental figure 6), although the small number of patients (n=4) impedes conclusions. Patients with FMF also reported improved VAS scores of

3.0 at baseline and 2.0 at Month 18. This trend was more prominent in those patients who had not received prior canakinumab therapy (7.0 at baseline and 0.5 at Month 18) (online supplemental figure 6).

Median AIDAI scores were stable and low for the majority of patients over time (figure 5). Among patients with all CAPS subtypes versus patients with NOMID/CINCA, the median patient-reported AIDAI scores were 4.0 and 3.5 versus 9.5 and 7.0 at baseline and interim analysis cut-off, respectively (figure 5). The median AIDAI score at Month 18 in the NOMID/ CINCA group of 26.0 should be interpreted with caution based on the small number of patients at this time point (n=4). In patients with FMF, AIDAI scores were stable and low for the majority of patients over time (figure 5).

Patients' assessment of current fatigue (VAS score) was generally low over time (online supplemental figure 7). Among patients with CAPS, median VAS scores were 3.0 and 1.0 at baseline and interim analysis cut-off, respectively (online supplemental figure 7); whereas in the more severe NOMID/CINCA subtype group, the equivalent scores were 2.0 and 4.0, respectively. Among patients with FMF, median VAS scores were reduced from 5.0 at baseline to 3.0 at the interim analysis cut-off (online supplemental figure 7).

The proportion of patients who reported days absent from school or work due to their disease generally increased over time (27.7% at baseline, 32.2% at Month 6, 34.1% at Month 24 and 58.6% at Month 30) (online supplemental table 8). The proportion of patients who reported that their social life was 'much impaired' by their disease was generally low over time (7.8% at baseline, 5.6% at Month 6, 6.3% at Month 24 and 21.7% at Month 30) (online supplemental table 9).
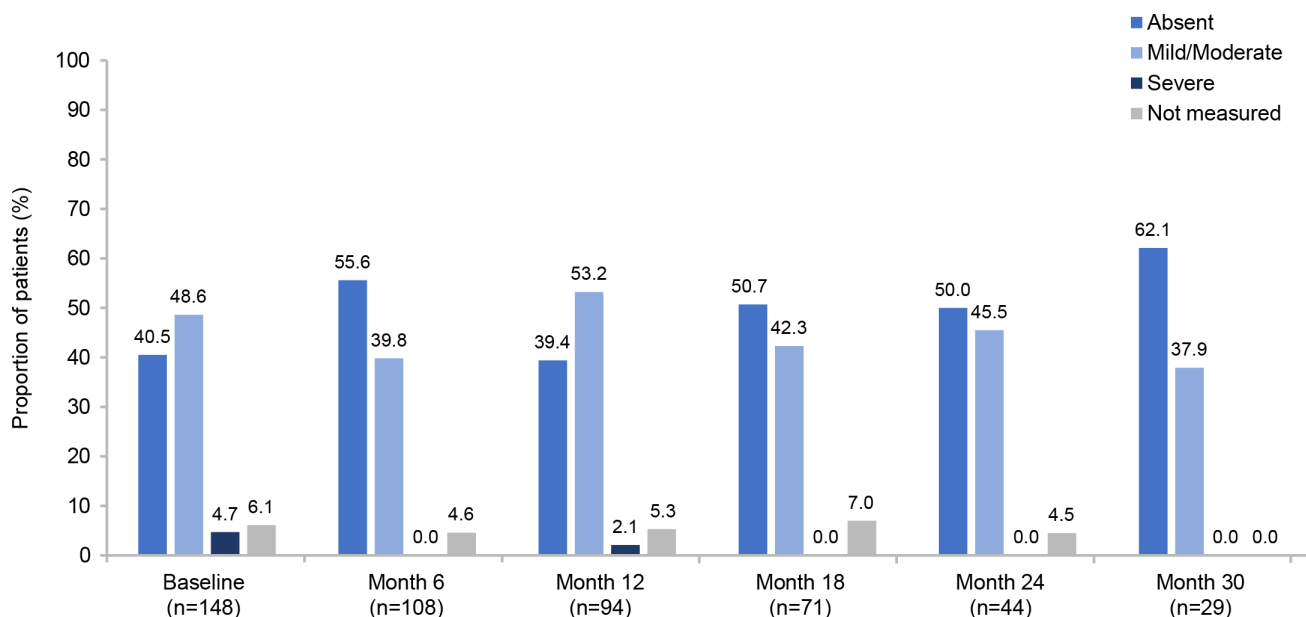
Figure 3 PGA of disease activity in the pooled population. Data were missing for 18, 14, 11, 5 patients at Baseline, Month 6, 12 and 18, respectively. PGA, physician's global assessment.
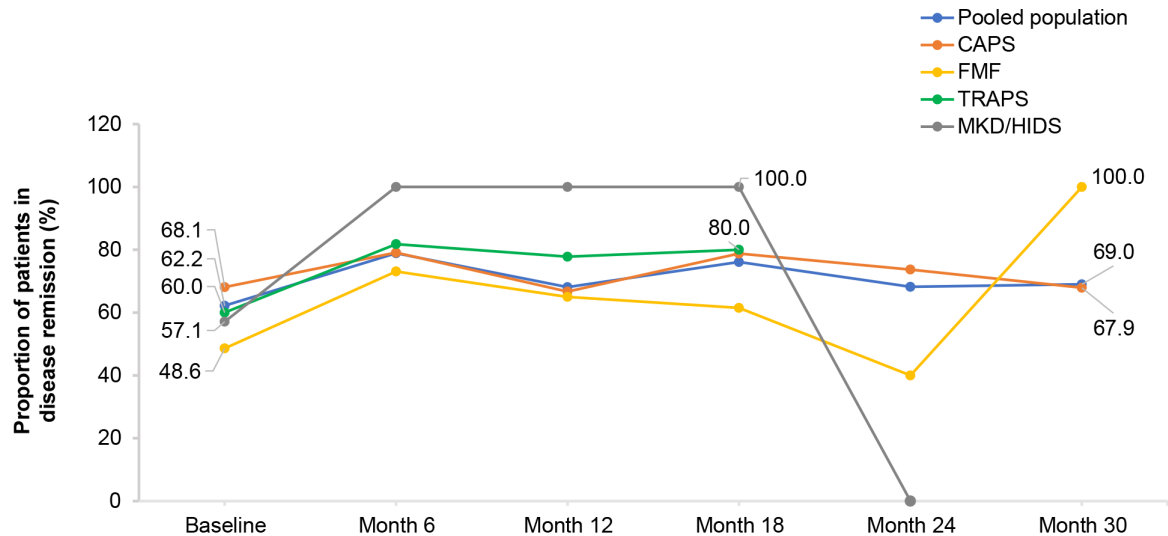
Figure 4 Physician's assessment of disease remission in the pooled population and individual disease cohorts (CAPS, FMF, TRAPS, MKD/HIDS). N=1 for the MKD/HIDS cohort at Month 24; as the patient was not in disease remission, the proportion is reported as 0%. CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

In the pooled paediatric population (aged 2 to <18 years old), median Z-scores for weight increased from 0.2 at baseline to 0.8 at Month 6 and remained stable over time. Similarly, median Z-scores for height for the paediatric population increased from −0.1 at baseline to 0.4 at Month 6 and remained stable over time (online supplemental figure 8).

The median (range) levels of CRP and SAA were stable and remained below the limits of normal (1 mg/dL) over time in the pooled population (CRP: 0.2 mg/dL (0.0–8.2) at baseline, 0.2 mg/dL (0.0–4.1) at Month 6 and 0.0 mg/dL (0.0–19.0) at Month 30; SAA: 0.5 mg/dL (0.0–119.0) at baseline, 0.4 mg/dL (0.1–48.0) at Month 6 and 0.2 mg/dL (0.1–1.5) at Month 30); median ESR remained stable over time (online supplemental figure 9). In patients with FMF who had no prior canakinumab therapy, median CRP and SAA levels were improved from baseline (CRP: 1.1 mg/dL; SAA: 6.8 mg/dL) to Month 6 (CRP: 0.1 mg/dL; SAA: 0.4 mg/dL).

The long-term effectiveness of canakinumab per dosing category was assessed over time (table 3). Effectiveness, as measured by control of disease activity, was comparable across all three dosing categories (<SD, SD, >SD) over the course of the study. Results for disease activity (assessed by patient and physician) of dosing groups for each disease cohorts are summarised in online supplemental table 10. Among patients with CAPS, FMF and TRAPS, CRP levels remained stable over time, indicating sustained disease control in all diseases. Nevertheless, across most outcome measures, disease activity was higher in patients with CAPS administered with SD or >SD canakinumab. In addition, patients' assessment of disease activity was generally higher in patients with FMF who received >SD canakinumab.

DISCUSSION

Data from the interim analysis of the RELIANCE registry presented in this manuscript confirm the long-term safety profile and effectiveness at controlling disease activity of canakinumab for the treatment of CAPS, FMF, TRAPS and MKD/HIDS. Disease activity was generally low and stable across all disease cohorts with most patients achieving sustained disease remission over time. Improvements were especially noticeable among patients with NOMID/CINCA and in the canakinumab naïve FMF cohort. Furthermore, inflammatory markers (CRP, SAA and ESR) generally remained within the limits of normal over time.

Some patients with CAPS can be affected by musculoskeletal pain, constant fatigue and common skin manifestations (including urticaria, rashes, lesions and patches), with even the mildest subtype of CAPS negatively impacting patients' professional lives and social activities. Accordingly, improvement in HRQoL is an important treatment goal for these diseases.[4 23 26–28] The results from this interim analysis highlight the sustained effect of canakinumab in controlling disease activity
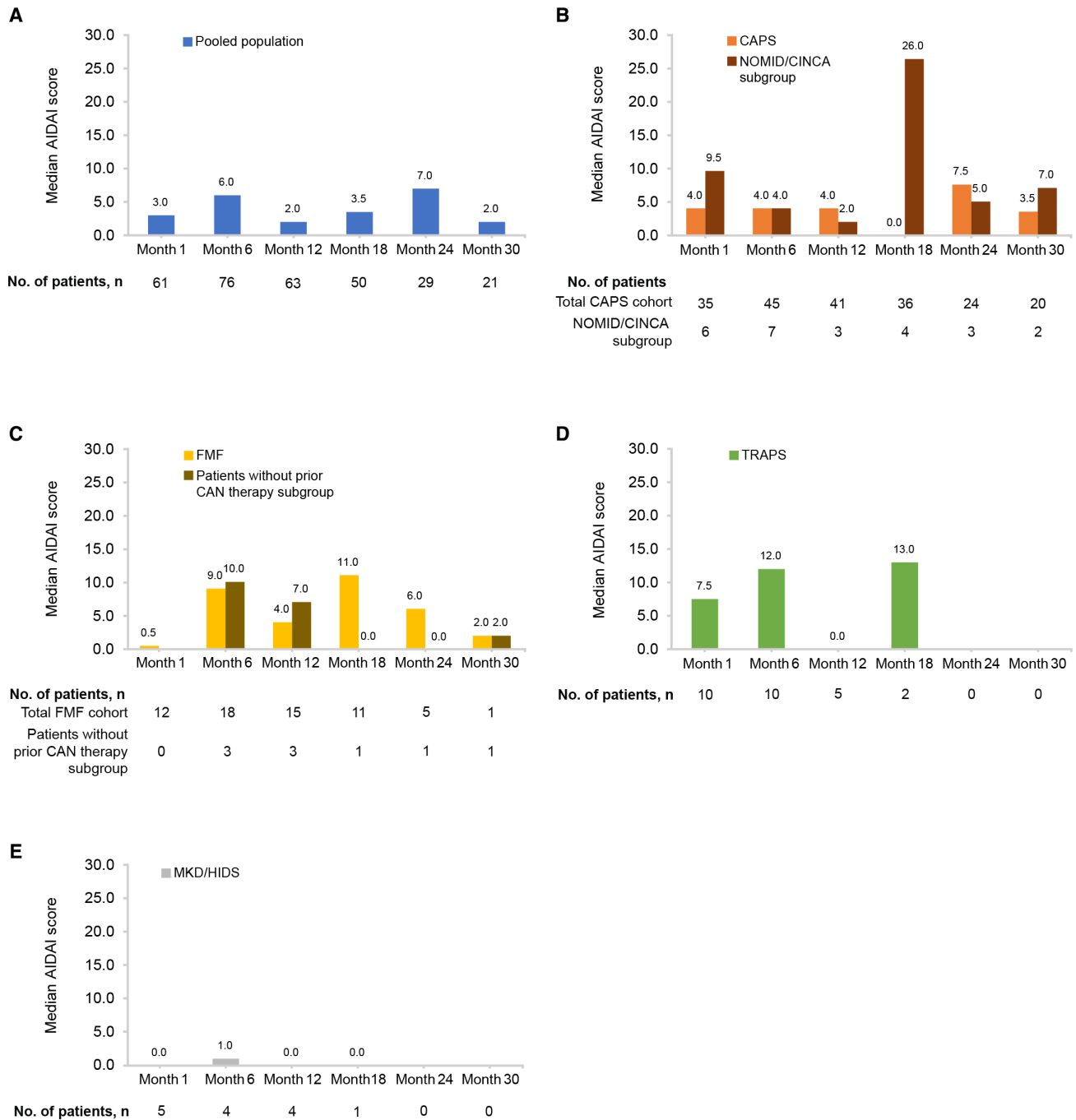
Figure 5 Median AIDAI score distribution over time in the (A) pooled population and individual disease cohorts (B) CAPS versus NOMID/CINCA subgroup*, (C) FMF versus patients without prior canakinumab therapy, (D) TRAPS and (E) MKD/HIDS. Active disease was defined as a total AIDAI score ≥9. *Includes patients diagnosed with MWS/NOMID, NOMID/CINCA, NOMID or CINCA; †No data were available for the patient cohort at this time point. AIDAI, autoinflammatory disease activity index diary; CAN, canakinumab; CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MWS, Muckle-Wells syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

(as measured by patient-reported outcomes), reflecting previous reports that canakinumab can improve HRQoL.[4] Furthermore, a trend in the stabilisation of growth patterns in the paediatric patient population was observed over time, suggesting that the control of inflammation in children may support physical development. In contrast to the generally well-controlled disease activity observed over the course of the registry, the proportion of patients who reported days absent from school or work due to their disease generally increased over time. While this appears contradictory, it highlights the fact that in these AID, clinical and laboratory disease activity is only one aspect in a whole spectrum of issues to be considered in comprehensive management. Factors like behavioural

Table 3 Efficacy outcomes (PGA of disease activity, patient's assessment of disease activity (VAS), CRP, SAA, ESR) for pooled population per dosing group

	<SD (N=33)	SD (N=46)	>SD (N=61)	Dose missing (N=28)
PGA of disease activity				
Baseline				
Absent	20 (60.6)	10 (31.3)	20 (33.9)	10 (41.7)
Mild/moderate	8 (24.2)	21 (65.6)	33 (55.9)	10 (41.7)
Severe	3 (9.1)	0 (0.0)	2 (3.4)	2 (8.3)
Not measured	2 (6.1)	1 (3.1)	4 (6.8)	2 (8.3)
Missing	0	14	2	2
Month 6				
Absent	17 (68.0)	14 (63.6)	25 (51.0)	4 (33.3)
Mild/moderate	5 (20.0)	8 (36.4)	24 (49.0)	6 (50.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not measured	3 (12.0)	0 (0.0)	0 (0.0)	2 (16.7)
Missing	0	8	3	3
Month 12				
Absent	12 (54.5)	7 (38.9)	13 (31.0)	5 (41.7)
Mild/moderate	9 (40.9)	10 (55.6)	24 (57.1)	7 (58.3)
Severe	1 (4.5)	0 (0.0)	1 (2.4)	0 (0.0)
Not measured	0 (0.0)	1 (5.6)	4 (9.5)	0 (0.0)
Missing	1	5	4	1
Month 18				
Absent	8 (50.0)	8 (72.7)	18 (48.6)	2 (28.6)
Mild/moderate	7 (43.8)	1 (9.1)	17 (45.9)	5 (71.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not measured	1 (6.3)	2 (18.2)	2 (5.4)	0 (0.0)
Missing	1	2	1	1
Month 24				
Absent	4 (40.0)	1 (33.3)	14 (53.8)	3 (60.0)
Mild/moderate	5 (50.0)	2 (66.7)	11 (42.3)	2 (40.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not measured	1 (10.0)	0 (0.0)	1 (3.8)	0 (0.0)
Month 30				
Absent	3 (100.0)	0 (0.0)	14 (63.6)	1 (50.0)
Mild/moderate	0 (0.0)	2 (100.0)	8 (36.4)	1 (50.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not measured	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient assessment of disease activity (VAS score)				
Baseline				
n	32	46	60	27
Median (Q1–Q3)	1.0 (0.0–3.0)	2.0 (0.0–4.0)	2.0 (0.0–4.0)	2.0 (1.0–6.0)
Month 6				
n	25	29	51	15
Median (Q1–Q3)	1.0 (0.0–2.0)	3.0 (0.0–4.0)	1.0 (0.0–3.0)	2.0 (0.0–4.0)
Month 12				
n	23	23	45	13

Continued

Table 3 Continued

	<SD (N=33)	SD (N=46)	>SD (N=61)	Dose missing (N=28)
Median (Q1–Q3)	1.0 (0.0–3.0)	3.0 (1.0–5.0)	2.0 (1.0–5.0)	1.0 (0.0–3.0)
Month 18				
n	17	13	38	8
Median (Q1–Q3)	2.0 (0.0–2.0)	3.0 (0.0–3.0)	1.0 (0.0–4.0)	1.5 (0.0–3.5)
Month 24				
n	10	3	26	5
Median (Q1–Q3)	0.0 (0.0–2.0)	4.0 (2.0–5.0)	1.0 (0.0–5.0)	3.0 (1.0–4.0)
Month 30				
n	3	2	22	2
Median (Q1–Q3)	0.0 (0.0–0.0)	2.0 (1.0–3.0)	0.0 (0.0–4.0)	0.0 (0.0–0.0)
CRP (mg/dL)				
Baseline				
n	33	40	57	24
Median (Q1–Q3)	0.3 (0.2–1.1)	0.3 (0.1–0.8)	0.1 (0.0–0.2)	0.2 (0.0–0.4)
Month 6				
n	25	26	49	14
Median (Q1–Q3)	0.3 (0.2–0.7)	0.3 (0.0–0.9)	0.1 (0.0–0.3)	0.1 (0.0–0.3)
Month 12				
n	23	20	42	12
Median (Q1–Q3)	0.5 (0.2–0.8)	0.2 (0.1–1.1)	0.0 (0.0–0.2)	0.0 (0.0–0.1)
Month 18				
n	16	12	36	8
Median (Q1–Q3)	0.2 (0.1–0.2)	0.2 (0.1–0.4)	0.1 (0.0–0.2)	0.0 (0.0–0.2)
Month 24				
n	9	3	24	5
Median (Q1–Q3)	0.3 (0.2–0.5)	0.2 (0.0–0.7)	0.1 (0.0–0.2)	0.0 (0.0–0.1)
Month 30				
n	3	2	22	2
Median (Q1–Q3)	0.0 (0.0–0.0)	0.3 (0.2–0.5)	0.0 (0.0–0.1)	0.2 (0.0–0.3)
SAA (mg/dL)				
Baseline				
n	30	35	50	22
Median (Q1–Q3)	0.60 (0.30–3.99)	0.67 (0.30–3.37)	0.30 (0.10–0.71)	0.40 (0.20–0.86)
Month 6				
n	23	24	46	14
Median (Q1–Q3)	0.73 (0.39–2.32)	0.54 (0.30–1.19)	0.30 (0.13–0.78)	0.30 (0.18–0.91)
Month 12				
n	21	20	39	9
Median (Q1–Q3)	0.80 (0.50–2.04)	0.79 (0.34–1.12)	0.40 (0.20–0.80)	0.30 (0.20–0.40)
Month 18				
n	13	10	33	7
Median (Q1–Q3)	0.70 (0.31–0.89)	0.45 (0.30–0.92)	0.30 (0.10–0.70)	0.20 (0.10–0.40)
Month 24				
n	8	3	23	5
Median (Q1–Q3)	0.50 (0.30–2.10)	0.50 (0.09–4.00)	0.30 (0.10–0.70)	0.20 (0.20–0.20)

Table 3 Continued

	<SD (N=33)	SD (N=46)	>SD (N=61)	Dose missing (N=28)
Month 30				
n	3	2	18	2
Median (Q1–Q3)	0.20 (0.10–0.30)	1.00 (0.50–1.50)	0.20 (0.10–0.40)	0.30 (0.30–0.30)
ESR (mm/hour)				
Baseline				
n	22	30	50	20
Median (Q1–Q3)	9.0 (5.0–18.0)	9.0 (5.0–17.0)	5.0 (4.0–7.0)	5.5 (4.0–12.5)
Month 6				
n	17	14	40	11
Median (Q1–Q3)	8.0 (5.0–11.0)	6.5 (2.0–10.0)	5.0 (3.0–8.0)	5.0 (2.0–8.0)
Month 12				
n	11	8	33	11
Median (Q1–Q3)	8.0 (6.0–8.0)	3.0 (2.0–8.0)	5.0 (4.0–6.0)	4.0 (2.0–5.0)
Month 18				
n	12	9	33	8
Median (Q1–Q3)	7.0 (6.0–9.0)	11.0 (9.0–12.0)	5.0 (3.0–5.0)	5.0 (2.5–5.0)
Month 24				
n	7	3	23	5
Median (Q1–Q3)	7.0 (6.0–12.0)	13.0 (3.0–17.0)	5.0 (2.0–7.0)	4.0 (2.0–4.0)
Month 30				
n	3	2	21	2
Median (Q1–Q3)	6.0 (5.0–6.0)	13.5 (9.0–18.0)	4.0 (4.0–6.0)	3.5 (2.0–5.0)

The SD of canakinumab was defined as 150 mg (or 2 mg/kg of body weight for patients weighing ≤40 kg) q8w for patients with CAPS, or 150 mg q4w for patients with FMF, TRAPS or MKD/HIDS. <SD was defined as canakinumab <130 mg q8w for patients with CAPS, or <130 mg q4w for patients with FMF, MKD/HIDS or TRAPS. >SD was defined as canakinumab >170 mg q8w for patients with CAP, or >170 mg q4w for patients with FMF, MKD/HIDS or TRAPS.
n, denotes the number of patients with available data at each timepoint.
CAPS, cryopyrin-associated periodic syndromes; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; PGA, physician's global assessment; qXw, every X weeks; SAA, serum amyloid A; SD, recommended starting dose; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; VAS, Visual Analogue Scale.

issues, role models within the family (eg, parents or siblings with AID), acceptance at school and workplace need to be addressed using psychosocial support.

Previous studies indicated that intensified dosing of canakinumab may be beneficial to achieve adequate disease control in patients with CAPS, particularly in children and patients with the most severe NOMID/CINCA subtype.[20 22 23] Results from this registry demonstrate that dose adjustment to >SD canakinumab can contribute to achieving disease control in those patients with CAPS, including most patients with NOMID/CINCA who on SD have persistent flares, as well as most paediatric patients (aged <12 years) with CAPS, TRAPS or MKD/HIDS.

Overall, no new or unexpected safety concerns were reported, which is in line with results from previous controlled studies and real-life registries of patients with AID.[15 17 18 23] AEs were common (60.1%), less so SAEs (13.1%) and SADRs (5.4%). The most common AEs were infections (32.7%). There were no reports of vertigo episodes across all disease cohorts, which had been a symptom identified in previous studies with patients with CAPS, mostly identified in NOMID/CINCA and MWS subtypes.[15 25] Some patients (n=7; 15%) reported adverse reactions to vaccination, which were suspected to be study drug-related but not classified as severe. This has also been reported previously in patients with CAPS, in particular to pneumococcal vaccination.[29] In total, four patients experienced suspected COVID-19 infection, with two patients experiencing confirmed COVID-19 infection and one death was recorded as COVID-19 related.

While long-term canakinumab treatment with >SD improved therapeutic effectiveness it also appeared to affect the frequency of SAEs and SADRs. This trend was observed in the CAPS cohort, in which serious infections and SADRs were more common in patients receiving >SD canakinumab, compared with lower

doses, and in paediatric patients aged between 12 and 18 years receiving >SD canakinumab, compared with other age groups (<4 years old, 12 to <18 years old, 18 to <65 years old and ≥65 years old). Although increased AEs were experienced more frequently with intensified doses of canakinumab during long-term treatment, no significant correlation could be identified due to the small number of patients experiencing these events. It should be noted that patients receiving >SD canakinumab would have high disease activity, a factor that could also contribute to an increase of observed SAEs. Nevertheless, these results suggest that further investigation is required and that continuous close monitoring and awareness in patients requiring >SD canakinumab treatment regimens is needed.

Adaptation of the canakinumab dose due to persistent disease activity was most common in patients with CAPS, perhaps because the benefits of treat-to-target strategies are more widely considered, studied and used in this cohort, than in other AID.[22 23 25] Moreover, it was observed that patients with severe CAPS subtypes (MWS and NOMID/CINCA) benefitted from higher doses of canakinumab. Higher disease activity was observed in the CAPS cohorts that had received SD or >SD of canakinumab, and an FMF subgroup of patients who received >SD canakinumab, suggesting that an intensified dosing regimen may be an important consideration for physicians treating patients with high disease activity. However, it should be noted that the intensified dose of canakinumab administered to patients with CAPS in absolute dose was equivalent to the recommended starting dose (150 mg (or 2 mg per kg of body weight for patients weighing 40 kg or less) administered subcutaneously q8w) given to patients with FMF, TRAPS and MKD/HIDS.

As with every real-world, observational study, limitations should be considered when evaluating the results from this interim analysis. Data collection from real-world disease registries are not controlled or conducted in a randomised fashion, meaning data are not comparable to those collected pre-registry and post-registry enrolment. Findings should be considered as an assessment of patient health condition over time. Furthermore, data were missing for a number of patients throughout the study leading to under-reporting of some patient outcomes due to loss of follow-up. In addition, as CAPS, FMF, TRAPS and MKD/HIDS are rare diseases, the patient population for some of the disease cohorts was small at specific time points, making it challenging to draw clear conclusions. As a number of patients with CAPS included in this analysis were pre-exposed to canakinumab in the β-Confident registry, this will have had an effect on the baseline data for these patients and should be considered when interpreting results. Some variables were not collected as part of the study, including the reason for dose increase of canakinumab, highlighting another limitation of this study.

In conclusion, results from the interim analysis of the RELIANCE registry, the longest running real-world canakinumab registry, confirm the long-term safety profile of canakinumab and its ability to control disease activity in the treatment of CAPS, FMF, TRAPS or MKD/HIDS. The results also highlight the importance of individual dose adjustments to achieve improvement of disease control and HRQoL.

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