Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome


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*Members of the Canakinumab in Cryopyrin-Associated Periodic Syndrome (CAPS) Study Group are listed in the Appendix.

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ABSTRACT

BACKGROUND

The cryopyrin-associated periodic syndrome (CAPS) is a rare inherited inflammatory disease associated with overproduction of interleukin-1. Canakinumab is a human anti–interleukin-1β monoclonal antibody.

METHODS

We performed a three-part, 48-week, double-blind, placebo-controlled, randomized withdrawal study of canakinumab in patients with CAPS. In part 1, 35 patients received 150 mg of canakinumab subcutaneously. Those with a complete response to treatment entered part 2 and were randomly assigned to receive either 150 mg of canakinumab or placebo every 8 weeks for up to 24 weeks. After the completion of part 2 or at the time of relapse, whichever occurred first, patients proceeded to part 3 and received at least two more doses of canakinumab. We evaluated therapeutic responses using disease-activity scores and analysis of levels of C-reactive protein (CRP) and serum amyloid A protein (SAA).

RESULTS

In part 1 of the study, 34 of the 35 patients (97%) had a complete response to canakinumab. Of these patients, 31 entered part 2, and all 15 patients receiving canakinumab remained in remission. Disease flares occurred in 13 of the 16 patients (81%) receiving placebo (P<0.001). At the end of part 2, median CRP and SAA values were normal (<10 mg per liter for both measures) in patients receiving canakinumab but were elevated in those receiving placebo (P<0.001 and P=0.002, respectively). Of the 31 patients, 28 (90%) completed part 3 in remission. In part 2, the incidence of suspected infections was greater in the canakinumab group than in the placebo group (P=0.03). Two serious adverse events occurred during treatment with canakinumab: one case of urosepsis and an episode of vertigo.

CONCLUSIONS

Treatment with subcutaneous canakinumab once every 8 weeks was associated with a rapid remission of symptoms in most patients with CAPS. (ClinicalTrials.gov number, NCT00465985.)
The cryopyrin-associated periodic syndrome (CAPS) comprises a spectrum of apparently distinct, rare, inherited inflammatory disorders of increasing severity, including the familial cold autoinflammatory syndrome, the Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disorder (also known as the chronic infantile neurologic, cutaneous, and articular syndrome). Patients with these disorders have severe fatigue, fever, and influenza-like myalgia from infancy, together with chronic anemia and inflammation of the skin, eyes, bones, joints, and meninges. Clinical features include rash, conjunctivitis, arthritis, chronic meningitis, sensorineural deafness, and intellectual impairment. Systemic AA amyloidosis that causes renal failure and usually results in death within 5 to 10 years develops in approximately 25% of patients.1–3

CAPS is associated with mutations in NLRP3, the gene encoding cryopyrin, a component of the interleukin-1 inflammasome that regulates the production of interleukin-1β.4–6 As a key proinflammatory cytokine mediating local and systemic responses to infection and tissue injury, interleukin-1β can induce a range of responses, including fever, pain sensitization, bone and cartilage destruction, and the acute-phase plasma protein response. The pivotal pathogenic role of interleukin-1 in CAPS has been demonstrated by the achievement of complete responses after treatment with the recombinant interleukin-1–receptor antagonist, anakinra.7–10

Canakinumab (ACZ885, Novartis Pharma) is a fully human anti–interleukin-1β monoclonal antibody that selectively blocks interleukin-1β and has no cross-reactivity with other characterized interleukin-1 family members, including interleukin-1α and interleukin-1Ra.11 A preliminary open-label study of canakinumab in patients with CAPS has been carried out.12–14 We describe here the response to treatment with canakinumab in patients with CAPS in a multicenter, randomized, double-blind, placebo-controlled clinical study.

METHODS

DOSE DETERMINATION

We selected a subcutaneous dose of 150 mg of canakinumab (or 2 mg per kilogram of body weight for patients weighing 40 kg [88 lb] or less) every 8 weeks on the basis of a pharmacokinetic and pharmacodynamic model showing a predicted relapse rate of 3% after the first dose and 1% subsequently.15 (For additional details, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STUDY DESIGN

The study, which was approved by the independent ethics committee at each participating center, consisted of three parts (Fig. 1 in the Supplementary Appendix). Part 1 was an open-label treatment period in which a single dose of canakinumab was administered; the response was assessed during the following 8 weeks. Part 2 was a double-blind withdrawal period, in which patients who had a sustained complete response in part 1 were randomly assigned to receive either canakinumab or placebo every 8 weeks for up to 24 weeks. At the end of part 2 or at the time of relapse, whichever occurred first, patients immediately entered the open-label part 3 of the study, in which they received canakinumab every 8 weeks for a minimum of 16 weeks, for a total study duration of 48 weeks.

All patients entering the study or their parents provided written informed consent. The sponsor (Novartis Pharma) funded the study and held the data. The investigators had unrestricted access to the data and to the analyses. All the authors vouch for the completeness and accuracy of the data and analyses presented. The decision to submit the manuscript for publication was made by the academic authors and the clinical communication leader at Novartis Pharma. Two of the academic authors wrote the first draft of the manuscript; all authors approved the final draft.

PATIENTS

Patients who had CAPS associated with an NLRP3 mutation and who required treatment were eligible for enrollment if they were between the ages of 4 and 75 years and weighed at least 15 kg (33 lb) but less than 100 kg (220 lb). Patients who had previously received treatment with anakinra, rilonacept, or canakinumab were eligible to participate immediately after such treatment had been discontinued and their disease had relapsed. Administration of other investigational biologic agents was not permitted during the 8 weeks before the baseline visit (for details, see the Supplementary Appendix).

ASSESSMENTS OF DISEASE ACTIVITY

At screening and monthly follow-up visits, physicians assessed global disease activity and each of
the following symptoms: urticarial rash, arthralgia, myalgia, headache or migraine, conjunctivitis, fatigue or malaise, and other symptoms related or unrelated to CAPS. The assessment was performed with the use of a 5-point scale for disease activity: absent, minimal, mild, moderate, or severe. Blood samples were collected to measure levels of acute-phase reactants, C-reactive protein (CRP), and serum amyloid A protein (SAA) and to assess hematologic and biochemical markers and immunogenicity. Blood samples were analyzed in a central laboratory by pathologists who were unaware of study-group assignments.

Patients performed a global assessment of their symptoms together with assessments of each of the following symptoms: fever or chills, rash, joint or muscle pain, eye discomfort or redness, fatigue, headache, and other symptoms. The assessments were performed with the use of the same 5-point scale used by physicians. Adverse events were recorded throughout the study; the severity of such events and their relationship to the administration of a study drug were recorded. Patients were asked about the occurrence of any injection-site reactions.

**STUDY DEFINITIONS**

A complete response to treatment was defined as a global assessment of no or minimal disease activity by a physician, an assessment of no or minimal rash, and a value for both serum CRP and SAA that was within the normal range (<10 mg per liter for both measures). Relapse was defined as a value for either CRP or SAA of more than 30 mg per liter, accompanied by a physician’s assessment of global disease activity that was greater than minimal or that was minimal and accompanied by a rash that was assessed as more than minimal. Patients in part 1 were eligible for entry into part 2 if they had had a complete response to canakinumab by day 15 with no relapse by week 8.

**OUTCOME MEASURES**

The primary outcome measure was the proportion of patients with a relapse of CAPS during canakinumab treatment, as compared with placebo, in part 2. Secondary outcome measures included the proportion of patients with a complete response in part 1, values of inflammatory markers, global assessments by physicians and patients, and safety and tolerability.

**STATISTICAL ANALYSIS**

The primary analysis was based on the intention-to-treat population in part 2. Patients who met the criteria for relapse or who discontinued treatment prematurely in part 2 for any reason were considered to have had a disease relapse. The study groups were compared with the use of a stratified Fisher’s exact test. The time until disease flare in part 2 was assessed with the use of a Cox proportional-hazards regression model. Kaplan–Meier estimates were plotted against time. Changes in inflammatory markers from week 8 were analyzed with the use of a stratified Wilcoxon rank-sum test. Fisher’s exact test was used to compare the incidence of infections between study groups in part 2. All statistical tests were two-sided at a significance level of 0.05.

**RESULTS**

**PATIENTS**

We screened 41 patients for entry in the study; of these patients, 6 were deemed to be ineligible (Fig. 2 in the Supplementary Appendix). Thus, 35 patients from 11 centers in five countries (France, Germany, India, the United Kingdom, and the United States) were enrolled in the study. Demographic and disease characteristics are summarized in Table 1.

**INITIAL OPEN-LABEL PHASE (PART 1)**

Of 35 patients enrolled in part 1, 34 (97%) had a complete response to treatment with a single dose of canakinumab, according to the protocol definition. Symptoms of CAPS diminished within 24 hours in patients who had a response (Fig. 1). A complete response was achieved by day 8 in 25 patients, by day 15 in 8 patients, and by day 29 in 1 patient. The patient who had a complete response on day 29 had a clinical response by day 15 but had elevated CRP and SAA values at this time, which were attributed to a self-limiting viral infection. The one patient who did not have a complete response had self-injected the medication. Canakinumab levels in this patient were substantially lower than expected and were consistent with administration of an incomplete dose. This patient was withdrawn from the study.

Three patients who had a complete response after a single dose of canakinumab did not proceed to part 2: one patient withdrew from the study because of a failure to maintain a satisfac-
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tory therapeutic response, and two others had mild conjunctivitis on the day of randomization and were reluctant to receive placebo. Thus, 31 patients (89%) proceeded to part 2.

Double-Blind Withdrawal Phase (Part 2)

Relapse
During the double-blind period, all 15 patients in the canakinumab group remained in remission. In contrast, 13 of the 16 patients (81%) in the placebo group had a disease flare (P<0.001). The median time until the disease flare was 100 days from the start of part 2 (i.e., approximately 22 weeks after the initial dose of canakinumab in part 1) (Fig. 2A).

Inflammatory Markers
CRP levels remained within the normal range among patients in the canakinumab group (median, 2.3 mg per liter) but rose in the placebo group (median, 24.4 mg per liter) (Table 2 and Fig. 2B). During the course of part 2, the mean increase in CRP level was 19.9 mg per liter in the placebo group, as compared with a mean increase of 1.1 mg per liter in the canakinumab group (P<0.001).

SAA levels remained within the normal range among patients in the canakinumab group (median, 6.1 mg per liter) but rose in the placebo group (median, 43.4 mg per liter) (Table 2). Over the course of part 2, the mean increase in SAA level was 71.1 mg per liter in the placebo group, as compared with a mean increase of 2.3 mg per liter in the canakinumab group (P=0.002).

Assessments of Disease Activity
By the end of part 2, all patients in the canakinumab group were rated as having no or mini-

Table 1. Demographic and Disease Characteristics of the Patients, According to Study-Group Assignment in Part 2.*

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Canakinumab (N=15)</td>
<td>Placebo (N=16)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — yr</td>
<td>34.0±14.9</td>
<td>33.4±16.1</td>
</tr>
<tr>
<td>Median — yr</td>
<td>36.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Range — yr</td>
<td>9–74</td>
<td>9–58</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
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<td></td>
</tr>
<tr>
<td>4–16 yr</td>
<td>4 (11)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>17–40 yr</td>
<td>17 (49)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>41–75 yr</td>
<td>14 (40)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>25 (71)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>White race — no. (%)†</td>
<td>33 (94)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>NLRP3 mutation — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R260W</td>
<td>18 (51)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>T348M</td>
<td>7 (20)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>D303N</td>
<td>3 (9)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>E311K</td>
<td>2 (6)</td>
<td>0</td>
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<tr>
<td>Other‡</td>
<td>5 (14)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Previous treatment — no. (%)</td>
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<td></td>
</tr>
<tr>
<td>Canakinumab</td>
<td>9 (26)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>17 (49)</td>
<td>5 (33)</td>
</tr>
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</table>

* Plus–minus values are means ±SD. All patients had the Muckle–Wells syndrome except for two who had the Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disorder. Percentages may not total 100 because of rounding.
† Race was determined by the investigator.
‡ Other mutations were M662T, A439V, D305N, T436N, and T436I.
mal disease activity by physicians, as compared with four patients (25%) in the placebo group (P<0.001). Rash was completely absent in 14 of 15 patients (93%) receiving canakinumab, as compared with 5 of 16 patients (31%) receiving placebo (Table 2).

At the end of part 2, 6 of 15 patients (40%) in the canakinumab group reported having a complete absence of symptoms, as compared with no patients in the placebo group (Table 2). Four patients in the canakinumab group reported having severe symptoms associated with other disorders: two patients in one household had acute gastroenteritis, a third patient had painful fibromyalgia, and a fourth had migraine (see Table 2 for details). No severe symptoms were reported by the patients in the placebo group at the end of part 2 (P=0.28 for the comparison between groups).

**SUBSEQUENT OPEN-LABEL PHASE (PART 3)**

All 31 patients from part 2 entered part 3, and 29 patients (94%) completed the protocol. Two patients discontinued therapy, one because of a therapeutic response that the patient considered to be unsatisfactory 138 days after entering the study and the other because of recurrent *Escherichia coli* urinary tract infections.

Clinical and biochemical remission of CAPS was sustained in 28 of the 29 patients (97%) who completed part 3. One patient had a relapse on the last day (day 336), 62 days after receiving the last dose of canakinumab. Among patients who received placebo in part 2 and were in a CAPS flare state on entry to part 3, CRP and SAA values decreased to medians of 2.3 and 5.8 mg per liter, respectively, at the end of the study. Median CRP and SAA values remained suppressed, at 1.9 and 5.1 mg per liter, respectively, in the 15 patients who received canakinumab throughout the study.

At the final assessment of part 3, a total of 30 of the 31 patients who had entered this final phase of the study (97%) had no or minimal disease activity, according to the assessment of physicians, and the remaining patient had mild disease activity. Rash was absent in 29 of the 31 patients (94%) and was minimal in the other 2 patients. Either no or minimal symptoms were reported by 26 of the 31 patients (84%), mild symptoms were reported by 1 patient, moderate symptoms by 2 patients, and severe symptoms by 1 patient, who also had fibromyalgia; data were missing for 1 patient.

**ADVERSE EVENTS**

No deaths or life-threatening adverse effects occurred. Two patients had serious adverse events while receiving canakinumab in part 3, and both of them discontinued therapy, as noted above. One of the two patients had a lower urinary tract infection requiring hospital admission; the other patient had an episode of vertigo accompanied by acute closed-angle glaucoma, which was attributable to CAPS, and withdrew from the study because of an unsatisfactory therapeutic effect. The use of canakinumab was not associated with any clear pattern of adverse events other than an increase in the rate of suspected infections (P=0.03).
(Table 3). The fact that the mean study-drug exposure in part 2 was greater in the canakinumab group (169 days) than in the placebo group (118 days) may have contributed to this increased incidence of suspected infections.

In parts 1 and 2, most patients (>91%) reported having no injection-site reactions; four patients reported a mild reaction. In part 2, a total of 13 of the 15 patients (87%) receiving canakinumab and 15 of the 16 patients (94%) receiving placebo reported no injection-site reactions. There were no reports of severe injection-site reactions. No immunogenicity against canakinumab was detected, and no safety issues emerged from hematologic monitoring, urinalysis, or other assessments (for details, see the Supplementary Appendix).

**DISCUSSION**

Our study of canakinumab showed rapid, substantial, and sustained clinical efficacy of this interleukin-1β inhibitor in patients with CAPS. The safety data, though limited, were generally reassuring, with only two serious adverse events occurring, no evidence of immunogenicity, and only occasional, mild injection-site reactions.

The beneficial effect of canakinumab on patients’ symptoms had a prolonged duration of action, probably because canakinumab has a plasma half-life of 28 to 30 days and perhaps because it has a disease-modifying effect through autocrine down-regulation of interleukin-1β production. Of the 35 patients who received canakinumab, 34 had a complete response after the administration of a single dose. At the end of the 24-week, double-blind, placebo-controlled phase, all patients who received canakinumab remained in remission, as compared with 25% of patients who received placebo. A noteworthy benefit of the complete clinical response to canakinumab and its associated effect in halting an extensive cascade of proinflammatory cytokine activity was a reduction of acute-phase SAA production to normal levels, which, in theory, should reduce the long-term risk of AA amyloidosis.

Symptom assessments by patients also showed a sustained benefit of canakinumab therapy, with 40% reporting a complete absence of symptoms, as compared with none in the placebo group. However, a limitation of the study, which was associated with its necessarily small size, was the presence of symptoms (headache, fever, and fatigue) attributed to non-CAPS disorders in four patients at the key time point at the end of part 2. As a result, patient-reported symptoms at this time did not differ significantly between the canakinumab group and the placebo group. Detailed examination of the records for these four patients revealed that they had all had a good response to canakinumab, and their physicians had rated their CAPS disease activity as absent or minimal in association with normal CRP and SAA measurements. At the end of part 3, a total

![Figure 2. Response to Canakinumab, as Compared with Placebo.](image-url)
### Table 2. Inflammatory Markers and Assessments by Physicians and Patients, According to Study-Group Assignment in Parts 2 and 3.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients Starting Part 1 (N=35)</th>
<th>Start of Part 1</th>
<th>Start of Part 2</th>
<th>End of Part 2</th>
<th>End of Part 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
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<td>C-reactive protein — mg/liter</td>
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<tr>
<td>Median</td>
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<td>19.6</td>
<td>26.0</td>
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<td>5.3</td>
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<tr>
<td>Range</td>
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<td>7.8–104.9</td>
<td>0.6–8.8</td>
<td>0.6–30.5</td>
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<td>P value for between-group comparison</td>
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<tr>
<td>Serum amyloid A — mg/liter</td>
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<td></td>
</tr>
<tr>
<td>Median</td>
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<td>48.2</td>
<td>111.9</td>
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<td>9.5</td>
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<tr>
<td>Range</td>
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<td>Disease activity — no. (%)</td>
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<tr>
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<td>9 (60)</td>
<td>8 (50)</td>
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<tr>
<td>Minimal</td>
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<td>1 (7)</td>
<td>0</td>
<td>4 (27)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Mild</td>
<td>7 (20)</td>
<td>2 (13)</td>
<td>5 (31)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
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<td>10 (67)</td>
<td>9 (56)</td>
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<td>0</td>
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<tr>
<td>Severe</td>
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<td>2 (12)</td>
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</tr>
<tr>
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<td>Rash — no. (%)</td>
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<tr>
<td>Absent</td>
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<td>1 (7)</td>
<td>2 (12)</td>
<td>13 (87)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Minimal</td>
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<td>3 (20)</td>
<td>3 (19)</td>
<td>2 (13)</td>
<td>3 (19)</td>
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<tr>
<td>Mild</td>
<td>9 (26)</td>
<td>4 (27)</td>
<td>5 (31)</td>
<td>0</td>
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<tr>
<td>Moderate</td>
<td>15 (43)</td>
<td>7 (47)</td>
<td>5 (31)</td>
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<td>0</td>
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<tr>
<td>Severe</td>
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<td>1 (6)</td>
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<tr>
<td>P value for between-group comparison†</td>
<td>&lt;0.001</td>
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Canakinumab in the Cryopyrin-Associated Periodic Syndrome

The New England Journal of Medicine

Assessment by patient

<table>
<thead>
<tr>
<th>Symptoms — no. (%)</th>
<th>Absent</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Missing data</th>
<th>P value for between-group comparison</th>
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<tbody>
<tr>
<td>4 (11)</td>
<td>2 (12)</td>
<td>6 (17)</td>
<td>8 (23)</td>
<td>9 (28)</td>
<td>4 (11)</td>
<td>4 (25)</td>
<td>0.28</td>
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</tbody>
</table>

*P values for the comparison between the canakinumab group and the placebo group in part 2 for global assessment of disease activity by physicians and global assessment of symptoms by patients.

† This P value was based on a post hoc analysis.

‡ For five patients, reported symptoms were found to be unrelated to the cryopyrin-associated periodic syndrome (CAPS). In addition, one of the patients had mechanical lumbar pain throughout the study related to a mild slipped disk, and reported severe joint or muscle pain and severe fatigue or low energy at the end of part 2. The third patient had a complete remission of CAPS symptoms after treatment with canakinumab but was found to have fibromyalgia, the symptoms of which had previously been masked by CAPS symptoms. This patient had mechanical lumbar pain throughout the study related to a mild slipped disk, and reported severe joint or muscle pain and severe fatigue or low energy at the end of part 2.

The efficacy of canakinumab in the treatment of CAPS demonstrates that interleukin-1β is an important factor in the pathogenesis of this disorder. The NLRP3 mutations that are associated with CAPS result in increased activity of the enzyme caspase-1, which increases secretion of interleukin-1β and downstream activation of other proinflammatory cytokines. Other interleukin-1 inhibitors (anakinra and rilonacept) also have demonstrated efficacy in CAPS. However, the prolonged duration of action of canakinumab and low incidence of injection-site reactions may confer certain advantages for canakinumab, since both anakinra and rilonacept are frequently associated with injection-site reactions, and both require more frequent administration (daily for anakinra and weekly for rilonacept).

In general, the infections seen in this small study were not serious, though suspected infec-
tions were significantly more prevalent in patients receiving canakinumab than in those receiving placebo. One patient had recurrent urinary tract infections with an antibiotic-resistant organism, which may have been affected by interleukin-1 blockade. Vigilance with respect to such infections will continue to be required. In conclusion, administration of canakinumab once every 8 weeks was associated with substantial control of inflammatory disease in children and adults with CAPS.

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APPENDIX

The following investigators were members of the Canakinumab in CAPS Study Group: S. Madhoo, UCL Medical School, London; J.-M. Berthelot, Hôtel Hôtel Dieu, Nantes, France; C. Jorgensen, Hôpital Lapeyronie, Montpellier, France; S. Morell-Dubois, Hôpital The following investigators were members of the Canakinumab in CAPS Study Group: S. Madhoo, UCL Medical School, London; J.-M. Berthelot, Hôtel Hôtel Dieu, Nantes, France; C. Jorgensen, Hôpital Lapeyronie, Montpellier, France; S. Morell-Dubois, Hôpital

REFERENCES


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Canakinumab (ACZ885, a fully human IgG1 anti-IL-1β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS)

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Abstract

Introduction: Cryopyrin-associated periodic syndrome (CAPS) represents a spectrum of three auto-inflammatory syndromes, familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA) with etiology linked to mutations in the NLRP3 gene resulting in elevated interleukin-1β (IL-1β) release. CAPS is a rare hereditary auto-inflammatory disease, which may start early in childhood and requires a life-long treatment. Canakinumab, a fully human anti-IL-1β antibody, produces sustained selective inhibition of IL-1β. This study was conducted to assess the efficacy, safety, and pharmacokinetics of canakinumab in the treatment of pediatric CAPS patients.

Methods: Seven pediatric patients (five children and two adolescents) with CAPS were enrolled in a phase II, open-label study of canakinumab in patients with CAPS. Canakinumab was administered at a dose of 2 mg/kg subcutaneously (s.c.) (for patients with body weight ≤ 40 kg) or 150 mg s.c. (for patients with body weight > 40 kg) with re-dosing upon each relapse. The primary efficacy variable was time to relapse following achievement of a complete response (defined as a global assessment of no or minimal disease activity and no or minimal rash and values for serum C-reactive protein (CRP) and/or serum amyloid A (SAA) within the normal range, < 10 mg/L).

Results: All patients achieved a complete response within seven days after the first dose of canakinumab and responses were reinduced on retreatment following relapse. Improvements in symptoms were evident within 24 hours after the first dose, according to physician assessments. The estimated median time to relapse was 49 days (95% CI 29 to 68) in children who received a dose of 2 mg/kg. Canakinumab was well tolerated. One serious adverse event, vertigo, was reported, but resolved during treatment.

Conclusions: Canakinumab, 2 mg/kg or 150 mg s.c., induced rapid and sustained clinical and biochemical responses in pediatric patients with CAPS.

Trial registration number: ClinicalTrials.gov: NCT00487708
Introduction
Cryopyrin-associated periodic syndrome (CAPS) comprises a spectrum of rare inherited chronic auto-inflammatory disorders including familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), neonatal onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurological, cutaneous, and articular syndrome (CINCA). Common characteristics of these disorders include high-grade fever, urticarial rash, ocular manifestations such as conjunctivitis, sensorineural hearing loss and arthritis [1-5].

Onset of symptoms generally occurs early in life, especially in patients with the two more severe phenotypes, MWS, and NOMID, and these disorders are associated with developmental abnormalities and progressive worsening of clinical manifestations such as sensorineural hearing loss and sight impairment [3-5]. In addition, the high levels of the acute phase protein, serum amyloid A protein (SAA) results in AA amyloidosis in approximately a quarter of patients with MWS, leading to renal impairment. Thus initiation of treatment in childhood is important for most patients and may reduce long-term sequelae.

All three phenotypes are associated with mutations in the NLRP3 gene encoding cryopyrin, also known as NALP3/CIA51 [1,6,7]. Cryopyrin is involved in the activation of interleukin (IL)-1β [8]. Mutations in NLRP3 are associated with over-activation of caspase-1, the enzyme which catalyses the cleavage of the precursor of IL-1β, pro-IL-1β, to generate active IL-1β in excess [9]. This suggested that IL-1β blockade might provide effective treatment for this rare disorder. Indeed studies with anakinra, a non-glycosylated form of the endogenous antagonist of the IL-1 receptor, IL-1Ra, and rilonacept, which binds to IL-1β with high affinity and thus blocks the binding of IL-1β to its receptor, have demonstrated promising therapeutic activity in patients with CAPS [10-12]. However, anakinra requires daily administration which can be difficult, especially for pediatric patients, and injections are frequently painful and can lead to injection site reactions and rash, while rilonacept is administered once weekly and is also frequently associated with injection site reactions. Both substances are not approved for the treatment of CAPS in children. There is, therefore, a need for improved anti-IL-1β therapies for the management of CAPS and other auto-inflammatory conditions driven by overproduction of IL-1β.

Canakinumab is a fully human IgG1 anti-IL-1β monoclonal antibody that binds to human IL-1β with high specificity and neutralizes the bioactivity of this cytokine [13]. It has a half-life of 21 to 28 days in adults [14] and produces rapid and sustained clinical remissions in patients with CAPS when dosed every eight weeks [15]. This paper reports efficacy, safety, and tolerability analysis of data of the seven pediatric patients (children or adolescents) out of 34 patients who were enrolled in a phase II, open-label study.

Materials and methods
Study design and intervention
This study involved patients (aged 4 to 75 years, body weight ≥12 and < 100 kg) with documented NLRP3 mutations and a clinical picture of CAPS requiring medical intervention. Patients with a very severe phenotype receiving steroid therapy could be included if they had received a stable dose for at least one week prior to the screening visit. Patients on anakinra after a washout period of 15 days post screening were allowed. Any anti-IL-1 therapy had to be discontinued before entering the study. Female patients of child bearing age were to use an effective method of contraception during the study and for at least three months after the last dose.

Patients received canakinumab at a dose of 2 mg/kg (body weight < 40 kg) or 150 mg s.c. (body weight ≥40 kg). Patients not achieving a complete response within seven days post initial s.c. treatment received a re-dose of canakinumab (5 or 10 mg/kg i.v.) as a rescue medication. Treatment including the possibility of a rescue i.v. dose was repeated upon each relapse.

The study was approved by the institutional review board/independent ethics committee and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained for all participants from parents or legal guardians and from patients, if appropriate.

Assessments
At baseline and at each study visit (post-treatment Day 1, Day 2, Week 1 and Week 5 of each treatment period), physicians assessed global disease activity and rash using a 5-point scale: absent, minimal, mild, moderate or severe. Blood samples were collected for assessment of CRP and SAA (at each study visit) and to assess hematological and biochemical markers (baseline, post-treatment Day 1, Day 2, Week 1, Week 5 and thereafter monthly each period) and immunogenicity (baseline, 1 day pre-dose, and Week 5 of each period).

Efficacy assessments
The primary efficacy variable was time-to-relapse after achieving a complete response. A complete response was defined as a global assessment of no or minimal disease activity and no or minimal rash, and CRP and/or SAA levels within the normal range (< 10 mg/L for both parameters). Relapse was defined as having a global assessment of disease activity of mild or greater or a global assessment of disease activity of minimal and an assessment of rash of mild or greater, plus CRP and/or SAA levels of > 30 mg/L.
Alternatively, for patients with low CRP/SAA levels at baseline relapse was defined by a clinical picture necessitating retreatment, based on physician’s global assessment of disease activity and rash. Secondary efficacy variables included the proportion of patients showing a complete response, physician assessments of disease activity, changes in levels of CRP and SAA.

**Pharmacokinetic assessments**
Canakinumab concentrations were assessed in serum by competitive ELISA assay (lower limit of quantification (LLOQ) = 100 ng/mL). Pharmacokinetic parameters were determined by non-compartmental analysis. IL-1β levels were analyzed as previously described [13].

**Safety assessments**
Adverse events (AEs) were monitored throughout the study. At each study visit, physicians asked patients for, or assessed (dosing visit), any local injection site reactions following s.c. administration. Other safety assessments included the regular monitoring of vital signs, hematology blood chemistry and urinalysis, and assays for anti-canakinumab antibodies using a binding BIA-core® assay (Biacore International AB, Rapsgatan 7, 754 50 Uppsala, Sweden) [16]. Height and weight were measured at baseline and at the end of the study.

**Statistical analysis**
A Weibull gap-time frailty model was used to estimate time-to-relapse for each dose regimen [17]. For patients who required an additional rescue dose of canakinumab, the dose regimen was defined as a separate group and the time-to-relapse was calculated from the time of i.v. rescue dose. Analyses were conducted using SAS software, version 8.2 (SAS Institute, Cary, NC, USA).

**Results**
A total of 34 patients were enrolled in this phase II, open-label study and the overall patient disposition is presented in (Figure 1). Here we report data for seven pediatric patients (five children aged 4 to 13 years with MWS and two adolescents, aged 16 and 17 years, with NOMID).

Demographics and baseline disease characteristics are summarized in table 1. Six patients had previously received anakinra and four had achieved a complete response; one other patient achieved a partial response and the sixth patient did not respond to anakinra. All five children received canakinumab at a dose of 2 mg/kg s.c. (with or without a rescue dose) while the two adolescents received canakinumab 150 mg s.c. All patients received at least one dose of canakinumab and the median number of doses received was six (range 1 to 20, including rescue doses). The total duration of exposure to canakinumab ranged from 126 to 463 days.

**Efficacy**
All patients achieved a complete response to their first dose of canakinumab and this was achieved within one day in four patients and within seven days in the

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*patient discontinued the study due to pregnancy

**Figure 1 Patient composition**
remaining three patients. Improvements in symptoms were evident in all patients within 24 hours of administration of canakinumab; at baseline all patients had moderate disease activity, while one day post-dose, disease activity was absent in four patients and minimal in the other three. CRP and SAA levels normalized within seven days in patients who had baseline values above the normal range (< 10 mg/L). The levels of CRP and SAA were maintained at normal levels in those patients who already had normal levels at baseline (Figure 2).

Six patients were retreated on relapse and four achieved a second complete response within seven days post-treatment and continued to achieve complete responses on retreatment with single doses of canakinumab on most occasions. Clinical relapses (that is, increase in both global assessment and skin assessment to mild or greater) were typically accompanied by an increase in SAA and possibly CRP to greater than 30 mg/L and this pattern was observed in both children and adolescents (Figure 3A, B). In one patient, clinical relapses were not accompanied by increases in SAA and/or CRP on most occasions (Figure 3C).

All five children on canakinumab 2 mg/kg s.c. achieved a complete response within seven days post initial dose. However, two patients with the V198M mutation relapsed within seven days in many treatment cycles and needed an i.v. rescue to achieve and maintain complete response (a rescue dose was administered in one patient after each s.c. dose and for the other patient on three occasions out of nine treatments). In these two patients with V198M mutation, rash and conjunctivitis were absent; symptoms of headache, abdominal pain, myalgia, and fever episodes in one patient were present, all being reversible.

The observed times to relapse for two adolescent patients receiving 150 mg s.c. were > 125 days in one who was discontinued after the first dose without experiencing a relapse and 86 days and 77 days in the second adolescent. Those values are in agreement with the

### Table 1 Demographics and baseline disease characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical picture/NALP3 mutation - Clinical symptom</th>
<th>Weight (kg)</th>
<th>CRP (mg/L)</th>
<th>SAA (mg/L)</th>
<th>Previous anakinra use/response</th>
<th>Physician’s global assessment of disease activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MWS/V198M - pyrexia, conjunctivitis, headache, abdominal pain, arthralgia and lassitude</td>
<td>17.2</td>
<td>8.2</td>
<td>1.8</td>
<td>Yes/No*</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>MWS/E311K- aphthae, stomach pain, fatigue, loss of energy, headache, conjunctivitis, myalgia, fever peaks, beginning of hearing deficit and arthralgia during night.</td>
<td>18.1</td>
<td>2.0</td>
<td>2.1</td>
<td>Yes/Partial**</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>MWS/T348M - Vomiting</td>
<td>23.3</td>
<td>3.90</td>
<td>14.0</td>
<td>Yes/Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>MWS/V198M - Low level of immunoglobulins, pyrexia, sensitivity to infection, coldness exposed, conjunctivitis, headache, oral aphthae, abdominal pain, myalgia and fatigue.</td>
<td>24.1</td>
<td>0.2</td>
<td>2.9</td>
<td>Yes/Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>5</td>
<td>MWS/E311K - exanthema, myalgia, conjunctivitis, attention deficit, headache, lack of concentration, oral aphthae, fatigue and hearing deficiency</td>
<td>35.3</td>
<td>9.9</td>
<td>14.1</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>6†</td>
<td>NOMID/T348M - urticarial rash, hepatomegaly, pyrexia, anemia, headache, stomach pain, malaise, nausea, fatigue, conjunctivitis, high frequency hearing loss (1 KHz), sterile meningitis, papilloedema, growth retardation, bilateral reduced visual acuity, knee arthritis, back pain, myalgia, leucocytes, and thrombocytosis</td>
<td>48.6</td>
<td>38.9</td>
<td>198.0</td>
<td>Yes/Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>7†</td>
<td>NOMID/G569R - exanthema, papillar edema, pseudo-tumor cerebri, hearing loss, arthritis, enlarged inner and outer liquor cavities, morphologically elevated bilateral intraocular pressure, and an enlarged blind spot in the visual field</td>
<td>52.0</td>
<td>65.6</td>
<td>151.0</td>
<td>Yes/Yes</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; SAA, Serum Amyloid A.

* Local lab values.
† The two adolescent patients had MWS/NOMID.

*No response - lack of efficacy while on anakinra.

**Partial response - MWS activity despite of anakinra therapy and necessity of anakinra dosage increase.
median time to relapse of 115 days (95% CI 94.1 to 136.4) estimated using a Weibull analysis in the group of adults and adolescent patients receiving 150 mg s.c. For children receiving 2 mg/kg s.c. the estimated median time to relapse was 49 (95% CI: 29.3 to 67.9) days (Table 2).

At study start, “fatigue”, which was part of the core variables for the physicians’ global assessment, was severe in two patients, moderate in three patients and mild in one patient. One day post-dose “fatigue” was absent in five patients and minimal in two patients and this was maintained until the patient experienced the next relapse.

PK/PD and IL-1β levels
The pharmacokinetic parameters for canakinumab are summarized in Table 3. Peak concentrations of 7.7 to 13.6 μg/mL were achieved in children receiving doses of 2 mg/kg (total dose, 35 to 96 mg) after 2 to 7 days and the apparent half life of canakinumab was 23 to 26 days. The rates of IL-1β production for the five MWS patients were 20.1 (Pt 1), 6.02 (Pt 2), 21.2 (Pt 3), 4.5 (Pt 4), and 5.8 (Pt 5) ng/day, and for the two NOMID patients 9.6 (Pt 6) and 16.7 (Pt 7) ng/day.

Safety
Canakinumab was generally well tolerated. All AEs were of mild to moderate severity. One serious AE (SAE) was reported, a case of vertigo (V198M, MWS) that resolved during treatment. The most frequently reported AEs were upper respiratory tract infections and rash (Table 4). One patient, aged 16 years, discontinued due to positive pregnancy test (pregnancy test was negative at enrolment and baseline). The pregnant adolescent was still in remission until day 126 (time of discontinuing the study). After discontinuation, the patient did not receive anakinra, and prednisone treatment (40 mg at first, then 20 mg daily based on the investigator’s assessment of disease condition) was started. Prednisone was partially effective without reaching serological remission (CRP levels 10 to 30 mg/L, SAA levels 13 to 75 mg/L). The pregnancy was uneventful and the newborn had a normal Apgar score at birth as well as all clinical findings were unremarkable. Injections were well tolerated. Three patients reported mild to moderate injection-site reactions; in total in six occasions from 54 injections. No anti-canakinumab antibodies were detected in any patients.

Markers of systemic inflammation such as white blood cell count, neutrophil count and platelet count were at the upper limit of normal at baseline and decreased within the first 24 hours post-dose.

Two children were anemic at baseline, and all children had normal hemoglobin levels at the end of the study. All other laboratory or biochemical markers (glucose, albumin, creatinine, total protein, creatine kinase, triglycerides, total cholesterol, serum glutamic oxaloacetic transaminases, serum glutamic pyruvic transaminases, and gamma-glutamyl transferase) showed little change over the course of the study. No clinically relevant changes in diastolic and systolic blood pressure or pulse were observed.

Over the course of the study, children gained in height and weight. The four younger children (4 to 7 years) who were treated on the study for 9 to 15 months gained 2.1 to 5.6 kg and the two for whom height data were available gained 4 cm in height. The fifth child, aged 13, was treated in the study for 12 months and gained 12.6 kg in weight (from 35.3 kg at study entry) and 9 cm in height (from 155 cm at baseline).
Figure 3 Response pattern in three patients: physician global assessment, physician skin assessment and CRP and SAA levels. In the upper and middle panels, the squares represent the physician’s assessment of global disease activity and rash. The shaded areas indicate absent and mild severity. In the lower panel, the concentrations of CRP (solid line, circle) and SAA (dotted line, triangle) are presented. The shaded area indicates a concentration of 0 to 30 mg/L. Vertical dotted lines on all panels indicate the time of re-dosing.
Table 3 Pharmacokinetic parameters following administration of the first dose of 150 mg or 2 mg/kg canakinumab

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>Cmax (μg/mL)</th>
<th>Tmax (d)</th>
<th>AUC0-∞ (μgd/mL)</th>
<th>t1/2 (d)</th>
<th>CL/F (L/d)</th>
<th>Vz/F (L)</th>
<th>CL/F/wt (L/d/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34.8</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>2</td>
<td>36.0</td>
<td>13.6</td>
<td>6.96</td>
<td>580</td>
<td>25.7</td>
<td>0.0621</td>
<td>2.3</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>46.6</td>
<td>7.67</td>
<td>2</td>
<td>543</td>
<td>23.7</td>
<td>0.131</td>
<td>4.48</td>
<td>0.0037</td>
</tr>
<tr>
<td>4</td>
<td>48.0</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>5</td>
<td>71.0</td>
<td>12.4</td>
<td>2</td>
<td>647</td>
<td>22.9</td>
<td>0.232</td>
<td>5.67</td>
<td>0.0048</td>
</tr>
<tr>
<td>6</td>
<td>150.0</td>
<td>16.3</td>
<td>7.05</td>
<td>211</td>
<td>22.9</td>
<td>0.232</td>
<td>5.67</td>
<td>0.0048</td>
</tr>
<tr>
<td>7</td>
<td>150.0</td>
<td>10.4</td>
<td>2.16</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

NE: : non-estimable.

Canakinumab Maximum (peak) serum drug concentration after drug administration; Tmax: Time to reach peak or maximum concentration following drug administration; AUC0-∞: Area under the concentration-time curve from time zero to infinity; t1/2: The elimination half-life associated with the terminal slope (0.2) of a semi logarithmic concentration-time curve; CL/F: The apparent total clearance from serum; Vz/F: The apparent volume of distribution during terminal phase.

Discussion

The results reported here indicate that canakinumab is a highly effective and well tolerated therapy for the treatment of CAPS in pediatric patients. All patients achieved complete clinical and biochemical responses within seven days of receiving the first dose of canakinumab and responses were rapidly re-induced on re-treatment after relapse in most patients. In addition, canakinumab was well tolerated in all patients.

This study included children who were younger than those enrolled in the previously conducted study in CAPS patients (31 adults and 4 children) receiving canakinumab 150 mg s.c. (body weight ≥40 kg) or 2 mg/kg s.c. (body weight < 40 kg), administered every eight weeks [15] and the results observed in both these studies were comparable thus extending the observations to children as young as four years old. In both studies, responses to canakinumab were rapid with improvements in symptoms being observed within 24 hours of administration of the first dose in most patients. In addition, most patients achieved a complete response within one week following administration of a single dose. Responses were sustained in most patients and were re-induced with a single dose of canakinumab on re-treatment.

In this study, the pharmacokinetics of canakinumab in pediatric patients was found to be similar to that in adults [18]. The half-life of canakinumab in children ranged from 23 to 26 days, comparable to that previously reported for adults with rheumatoid arthritis (that is, 21 to 28 days) [14] and for adults with CAPS (26 days) [13,15]. This supports every eight-week dosing in children as in adults, which was shown to produce sustained remissions in the phase III study which included four children. This compares favourably with the very short half-life of anakinra (four to six hours) [19] and half-life of 6.3 days in children and 7 days in the adult population for rilonacept [20]. As a result of its very short half-life, anakinra is administered once daily while rilonacept is administered once weekly. This need for frequent injections is an important shortcoming of these medications, especially for children who may well be afraid of needles and do not understand the importance of their medication. The prolonged half-life of canakinumab allows sustained remissions to be achieved with eight-weekly dosing and, therefore, represents a major step forward in the management of this debilitating disorder.

The estimated median time-to-relapse in this study ranged from approximately 50 days in children receiving a dose of 2 mg/kg s.c. to 115 days in adolescents and adults receiving a dose of 150 mg s.c. Thus the estimated time-to-relapse in children was approximately half that for adults. This does not fit with the pharmacokinetic data for canakinumab reported for this study, which show the pharmacokinetics of canakinumab in pediatric patients to be similar to those in adults and suggests that factors other than pharmacokinetics of canakinumab may have contributed to the difference in time-to-relapse. Two children with CAPS symptoms did not have elevated CRP/SAA levels at baseline and were diagnosed for V198M. One of these patients failed to achieve complete response with a single s.c. dose on a number of occasions and both patients were frequently re-dosed (residual disease symptoms with anakinra treatment (dose increased over the first months in one patient and over the first year in second patient) and frequent necessity of dosage increase to anakinra was recorded in the medical history). V198M mutation has
been described as inducing CAPS with a heterogeneous phenotype which variably responds to increasing doses of anti IL-1 medication [21-23]. In addition, Aksentijevich et al. reported a patient with a V198M variant who did not adequately respond to anakinra treatment and discussed that other so far unknown genetic factors may be involved in the disease phenotype [24]. Thus, it is possible that patients with particular mutations such as the V198M mutation may require higher doses of canakinumab or more frequent administration to maintain their response and have contributed to the lower value for time-to-relapse for children reported for this study.

In this study, six patients received anakinra treatment prior to enrolment. Four were complete responders, one patient responded partially and one patient failed to respond to anakinra therapy. The fact that both the partial and non-responder patients achieved a complete response to canakinumab is thus encouraging.

In addition to achieving sustained clinical remissions, most pediatric patients achieved sustained normalization of CRP and SAA levels. This is likely to have important implications for the long-term outcome of patients since prolonged elevation of SAA levels is associated with the development of AA amyloidosis which severely impairs renal function and leads to renal failure and death if effective therapy is not given. A recent study of patients with systemic juvenile idiopathic arthritis (SJIA) found to gain in height and weight, suggesting that canakinumab by inhibiting the catabolic state linked to chronic inflammation allows normal development in the children.

All children showed rapid improvement of fatigue following treatment, which is a great advantage for their quality of life. Reduced fatigue leads to improved receptiveness in school and is a major advantage in development.

The data reported here indicate that canakinumab is well tolerated in children and adolescents, as well as in adults, as reported previously [15] and elsewhere for this study [13]. All adverse events were mild or moderate in severity and only one SAE, a case of vertigo that resolved during treatment, was reported. These data support those previously reported for the placebo-controlled phase of the phase III study [15]. In addition, in both studies [13,15] few patients reported injection site reactions and none of these were severe. This contrasts with anakinra and rilonacept; in studies in patients with CAPS, approximately half of patients experienced injection-site reactions and an increased risk of infections was observed [10,11,26]. In this study, children were found to gain in height and weight, suggesting that canakinumab by inhibiting the catabolic state linked to chronic inflammation allows normal development in the children.

The results of this study provide an important confirmation of the efficacy of canakinumab in children with this rare disorder and suggest that the safety profile of canakinumab in pediatric patients is similar to that in adults. Safety data for canakinumab in children have also been reported for doses of 0.5 to 9 mg/kg in children with systemic juvenile idiopathic arthritis (SJIA) and confirm the favourable safety profile of canakinumab in children [27].

However, the results reported here are necessarily limited since they are based on only seven pediatric patients in a non controlled study. Also, the definition of relapse remains elusive in auto-inflammatory disease purely on clinical grounds. Although the efficacy and safety of canakinumab for the treatment of pediatric CAPS patients is confirmed in this study, the long-term impact of canakinumab treatment on the course of the disease still needs to be addressed further. In addition, further research is warranted in CAPS patients who have the V198M mutation to understand why they require higher doses of canakinumab or more frequent administration to maintain their response.

Recently, canakinumab was approved by EMA for treatment of CAPS and by the FDA for FCAS and MWS in adult and pediatric patients [28,29], giving physicians an important new therapy for the management of this debilitating disorder. Early diagnosis and prompt initiation of treatment should enable children with this rare disorder to live a more normal life and may reduce the risk of long-term sequelae, such as progressive loss of vision and hearing and development of renal insufficiency.
Conclusions
Canakinumab is an effective, well tolerated therapy for pediatric patients with CAPS.

Abbreviations
AEs: adverse events; CAPS: cryopyrin-associated periodic syndrome; CI: confidence interval; CIAS1: 5’-interleukin-1β promoter; CIASI: chronic infantile neurological cutaneous and articular syndrome; CRP: serum C-reactive protein; CXC: familial cold auto-inflammatory syndrome; i.v.: intravenously; IL-1β: interleukin-1β; LLOQ: lower limit of quantification; MWS: Muckle-Wells syndrome; NOMID: neonatal-onset multisystem inflammatory disease; s.c.: subcutaneously; SAA: serum amyloid A protein; SAEs: serious adverse events; SJIA: systemic juvenile idiopathic arthritis.

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Competing interests
JKD is a consultant for Novartis Pharma and has received research grants and honorarium for lectures/symposiums. NB is a consultant for Novartis Pharma. SDF, TJ, KS, AC, ST, AMW and CR are employees of Novartis Pharma and own stock options in the company, and the company holds patents for the drug molecule.

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Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever

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Abstract

Introduction: This open-label pilot study aimed to investigate the efficacy of canakinumab in colchicine-resistant familial Mediterranean fever (FMF) patients.

Method: Patients with one or more attacks in a month in the preceding 3 months despite colchicine were eligible to enter a 30-day run-in period. Patients who had an attack during the first run-in period advanced to a second 30-day period. At the first attack, patients started to receive three canakinumab 150 mg subcutaneous injections at 4-week intervals, and were then followed for an additional 2 months. Primary efficacy outcome measure was the proportion of patients with 50 % or more reduction in attack frequency. Secondary outcome measures included time to next attack following last canakinumab dose and changes in quality of life assessed by SF-36.

Results: Thirteen patients were enrolled in the run-in period and 9 advanced to the treatment period. All 9 patients achieved a 50 % or more reduction in attack frequency, and only one patient had an attack during the treatment period. C-reactive protein and serum amyloid A protein levels remained low throughout the treatment period. Significant improvement was observed in both physical and mental component scores of the Short Form-36 at Day 8. Five patients had an attack during the 2-month follow-up, occurring median 71 (range, 31 to 78) days after the last dose. Adverse events were similar to those observed in the previous canakinumab trials.

Conclusion: Canakinumab was effective at controlling the attack recurrence in patients with FMF resistant to colchicine. Further investigations are warranted to explore canakinumab’s potential in the treatment of patients with colchicine resistant FMF.

Trial registration: ClinicalTrials.gov NCT01088880. Registered 16 March 2010.

Introduction

Familial Mediterranean fever (FMF), the most common form of hereditary autoinflammatory disorder, is characterized by recurrent attacks of fever with serosal or synovial inflammation, generally lasting 12 to 72 hours [1]. It has also been associated with increased risk of secondary amyloidosis, mainly affecting renal and vascular function in untreated or insufficiently treated patients with FMF.

Colchicine, the standard of care for patients with FMF, has been considered as safe and effective in the majority of the patients for reducing both the frequency of inflammatory episodes and the risk of developing amyloidosis [2–4]. However, there are currently no effective and approved alternatives for FMF patients who are intolerant to colchicine, and dose reductions due to adverse effects may result in diminished efficacy. In addition, approximately 5–10 % of patients with FMF continue to have frequent inflammatory episodes despite receiving the highest tolerable doses (1.5 to 2.0 mg/day) of colchicine, which are considered to be within the effective range.

The majority of FMF patients have autosomal recessive inheritance associated with mutations in the MEFV gene, which encodes pyrin protein [1]. FMF-related MEFV mutations, which affect pyrin-mediated regulation of caspase 1 activity in the inflammasomes, are
associated with increased IL-1β production in mice and humans [1]. Therefore, inhibition of IL-1 activity may decrease both frequency and severity of acute attacks in patients with FMF. Several reports of patients with FMF being successfully treated with agents blocking IL-1 activity, mainly with daily injections of the recombinant form of IL-1 receptor antagonist (IL-1Ra), anakinra, have confirmed the critical role of IL-1 in the pathogenesis of FMF [5, 6].

The objective of this study was to evaluate the efficacy and safety of canakinumab, a fully human anti-IL-1β monoclonal antibody with a half-life of approximately 4 weeks, that binds to human IL-1β and neutralizes its proinflammatory effects, in adolescent and adult patients with FMF, who are resistant or intolerant to higher doses of colchicine.

**Methods**

The present study was an investigator-initiated, open-label exploratory trial that included adolescent and adult FMF patients with active disease despite receiving the highest tolerable doses of colchicine (1.5 to 2.0 mg/day). All patients had a typical type 1 phenotype, fulfilling the criteria for FMF diagnosis [7], along with at least one of the exon 10 mutations in the MEFV gene. Patients with end-organ dysfunction due to secondary amyloidosis, active tuberculosis or any other infectious diseases, or a history of malignancy within the last 5 years were excluded from the study.

Colchicine-compliant patients with a history of one or more attacks per month within 3 months before the screening were eligible to enter the first 30-day run-in period. Patients who had at least one attack during that period advanced to a second 30-day period, and they received their first dose of canakinumab upon the first attack they experienced during this second 30-day run-in period.

The treatment period started with the first injection, and patients received a total of three subcutaneous injections of canakinumab 150 mg at 4-week intervals. The canakinumab dose could be increased to 300 mg, if an attack occurred between the first and second doses. Stable doses of colchicine (1.5 to 2.0 mg/day) were allowed throughout the study without any dose modification, and compliance was followed tightly throughout the study. After the 12-week treatment period, the patients were subsequently followed for up to 2 months or until the next attack.

FMF attacks were confirmed by presence of fever, clinical findings of serositis/arthritis, and elevated C-reactive protein (CRP) levels. Details of each attack (duration, type, severity, maximum body temperature) were recorded in diaries. Diaries were dispensed to the colchicine-resistant FMF (crFMF) patients at each visit to record the occurrence of any attacks between the scheduled visits.

The primary outcome measure was the proportion of patients with 50% or more reduction in time-adjusted frequency of attacks. Due to the unequal pre-treatment and treatment periods, attack rates were adjusted to the 84-day treatment period compared with the pre-treatment periods. Secondary outcome measures included the percentage of patients with no attacks in the treatment period, time to next attack after the last canakinumab administration, changes in quality of life assessed by the 36-item short-form health survey (SF-36), and serum levels of CRP and serum amyloid A (SAA) proteins. Physicians’ and patients’ global assessments of control of FMF since the last visit and response to treatment at the end of the treatment period were also measured using a modified 5-point scale [8]. All adverse events and laboratory values were recorded at each visit for the assessment of safety of canakinumab treatment.

Istanbul Faculty of Medicine Ethics Committee and Ministry of Health approved the study protocol, and all patients provided written informed consent before the screening. Exploratory analyses were performed using descriptive statistics.

**Results and discussion**

A total of 13 patients with crFMF were screened and included in the first 30-day run-in period. Nine patients (median age 22 years, range, 12 to 34) had ≥1 attack during that period, advancing to the second 30-day period, and began their treatment period by starting canakinumab treatment at the first observed attack within this period. Patient baseline demographic characteristics and MEFV genotypes are summarized in Additional file 1: Table S1.

All nine patients in the treatment period achieved the primary endpoint of ≥50% reduction in frequency of attacks compared with the time-adjusted pre-treatment frequency of attacks. During the treatment period, only one patient, who was p.Met694Val homozygous and receiving 2 mg/day colchicine, had an attack of peritonitis on day 54. No patient qualified for a canakinumab dose increase between the first and second injections. The time-adjusted frequency of attacks over 84 days observed in the screening and run-in periods, including the baseline attack (median 3.29, range 2.47 to 4.2), decreased dramatically during the treatment period (median 0, mean 0.11).

Five patients, all p.Met694Val homozygous and receiving 2 mg/day colchicine, subsequently experienced an attack within the 2-month follow up, which occurred at a median 71 days (range 31 to 78 days) after the last canakinumab injection (Fig. 1). Median baseline CRP and SAA levels (58 mg/L and 162 mg/L, respectively) on day 1 of canakinumab administration normalized (2.5 mg/L...
and 5.8 mg/L, respectively) by day 8, and remained low throughout the study (Additional file 2: Figure S1). No other significant laboratory abnormalities were noted.

The median SF-36 physical and mental component scores increased dramatically at day 8 compared with baseline scores and continued to improve throughout the treatment period (Additional file 3: Figure S2). Compared with baseline, the physician’s and patient’s global assessment of crFMF control improved with canakinumab treatment, and overall treatment response was reported as being very good both by physicians (for all patients) and patients (seven of nine patients) at the end of study (Fig. 2).

Eight patients reported at least one adverse event; headache (n = 4) and upper respiratory tract infection (n = 2) were the only adverse events reported by more than one patient (Table 1). All adverse events were mild or moderate except one, which was a severe headache. None of the patients discontinued the trial due to an adverse event. A mild, local injection-site reaction was recorded in two patients on at least one occasion.

One of the patients became pregnant during the treatment period after the third canakinumab dose and gave birth to a healthy son.

This open-label pilot trial showed that monthly canakinumab 150 mg subcutaneous injections prevented attacks in patients with crFMF, and only one of nine patients experienced an attack during canakinumab treatment. The safety profile of canakinumab in this small group of patients was similar to that of larger controlled trials in other hereditary autoinflammatory conditions [8–10].

Colchicine has long been used to prevent inflammatory attacks and reduce the risk of secondary amyloidosis in patients with FMF. Despite the efficacy of colchicine, some manifestations, such as arthritis, are less responsive to colchicine [11]. Furthermore, 5–10% of patients are non-responders to colchicine [12], and the number of...
FMF patients who are either intolerant or resistant to colchicine and continue to experience frequent and/or severe inflammatory attacks is increasing [13].

Given the association of type and number of MEFV variations with increased production of IL-1β, several case reports of patients treated with either anakinra or canakinumab have suggested the potential efficacy of IL-1 blockade in colchicine-resistant patients and those with amyloidosis [5, 6]. Additionally, in a recent randomized, double-blind, alternating-treatment trial the frequency of attacks decreased with weekly injections of rilonacept, another anti-IL-1 drug, consisting of humanized IL-1 receptor, IL-1 receptor accessory protein and the Fc portion of IgG1 [14]. All three drugs block IL-1 beta activity, but there are some differences, mainly resulting from the half-lives of these drugs, the shortest being for anakinra, requiring injections at least once daily, and the longest being for canakinumab, requiring monthly or bi-monthly injection intervals, which may affect the quality of life of patients. There is no study comparing the dynamics of IL-1 beta secretion in patients with crFMF with those in patients with cryopyrin-associated periodic fever syndrome (CAPS) [8, 9]. Therefore, in this pilot trial, we aimed to test the efficacy and safety of canakinumab in patients with crFMF by 4-weekly administration intervals for 3 months and followed them up for 2 months to observe any recurrence of inflammatory attacks. In this follow-up period there was an inter-individual variability in the timing of recurrent attacks, with a range of 31 to 78 days after the last dose in five patients, and possibly reflecting differences in their inflammatory activity. Randomized controlled trials are expected to provide further data about the optimum dosage and administration intervals of canakinumab in patients with crFMF.

The limitations of this small exploratory study were its open-label design, relatively short treatment period, and lack of formal definitions for disease severity and colchicine resistance. However, inclusion of mainly patients with FMF with two penetrant mutations and ≥1 attack per month despite receiving the highest tolerable doses of colchicine, together with confirmation of attacks and colchicine-compliance during the run-in period, represent a real-world patient cohort with few treatment options.

Conclusions

In conclusion, the results of the present pilot trial suggest that canakinumab may be an effective and safe treatment option for colchicine-resistant and colchicine-intolerant patients with FMF, and warrant further investigations to explore its efficacy, safety and optimum dosage and administration intervals in this subset of FMF patients.

Additional files

Additional file 1: Table S1. Demographics and baseline characteristics of the patients with familial Mediterranean fever (FMF) during the enrollment into the treatment period (n = 9). CRP C-reactive protein, ESR erythrocyte sedimentation rate, SAA serum amyloid A. (DOCX 16 kb)

Additional file 2: Figure S1. Serum C-reactive protein (CRP) and serum amyloid A (SAA) measurements during the treatment and follow-up periods. EOS end of study. (DOCX 61 kb)

Additional file 3: Figure S2. Short form-36 (SF-36) physical component summary (PCS) and mental component summary (MCS) scores during the treatment and follow-up periods. EOS end of study. (DOCX 53 kb)

Abbreviations
crFMF: colchicine-resistant familial Mediterranean fever; CRP: C-reactive protein; FMF: familial Mediterranean fever; IL-1: interleukin-1; SAA: serum amyloid A; SF-36: Short form-36.

Competing interests

A. Güls, H. Ozdoğan and O. Kasapcopur received research grants and honorariums from Novartis Pharmaceutical Corporation. B. Erer and S. Ugurlu have no conflict of interest; and S. Sevgi and N. Davis are employees of Novartis Pharmaceutical Corporation. None of the authors have non-financial competing interests.

Authors’ contributions

AG conceived of the study, and participated in its design, coordination and analysis of the results; and he helped to draft the manuscript. HO and OK participated in its coordination and helped to analyze the data and draft the manuscript. BE and SU participated in the coordination and execution of the trial and revised the manuscript. SS and ND participated in the design, coordination and analysis of the results; and he helped to draft the manuscript. HO and OK contributed and approved the final manuscript; and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

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Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study

Familial Mediterranean fever (FMF), the most common monogenic autoinflammatory disease, is characterized by recurrent self-limited attacks of fever and serositis. Between 5% and 10% of patients are resistant to or intolerant of colchicine, the current standard of care (1). Pyrin, the mutated protein in FMF, has an important role in the regulation of interleukin-1β (IL-1β) activation. This knowledge has led to the effective use of IL-1 inhibitors in >50 reported patients with colchicine-resistant FMF, including in one controlled study (2,3). In the present study we assessed the efficacy and safety of canakinumab, a selective, fully human anti–IL-1β monoclonal antibody with a terminal half-life of 500–34 days, in the treatment of children with colchicine-resistant FMF.

This 6-month, phase II, open-label, single-arm study (clinicaltrials.gov identifier NCT01148797) was conducted in 7 Caucasian children with FMF (5 boys and 2 girls; median age 9.5 years [range 6.8–14.9]) at 2 centers in Israel (Rambam Medical Center and Shaare Zedek Medical Center). The study was approved by the ethics committees at both hospitals, and informed consent was obtained from the parents/legal guardians of the participants. Participants were diagnosed according to the Tel-Hashomer criteria (4), with 2 exon 10 mutations on the MEFV gene (M694V/M694V in 5, M694V/V726A in 1, and M694V/M680I in 1). Participants were all colchicine resistant, having had ≥3 well-documented acute FMF attacks during the 3 months prior to screening despite treatment with colchicine at ≥1–2 mg/day (based on age) for at least 3 months.

Following successful screening, participants were enrolled in a 30-day run-in period. Those who experienced ≥1 investigator-confirmed FMF attack during this time were eligible for treatment. In addition to continuing daily colchicine treatment at the usual dosage, participants received 3 subcutaneous injections (4 weeks apart) of canakinumab 2 mg/kg (maximum 150 mg), with the first injection (day 1) administered during the next attack following the run-in period. The dose was doubled to 4 mg/kg (maximum 300 mg) if an attack occurred between the day 1 and day 29 visits. Day 86 was considered the end of the treatment period (4 weeks after administration of the last dose of canakinumab). Participants were followed up for another 2 visits (that occurred between day 126 and 160) or until an attack occurred (whichever occurred first). Attacks were then treated with acetaminophen and/or nonsteroidal antiinflammatory drugs only. The primary outcome measure was the proportion of participants with ≥50% reduction in the frequency of FMF attacks during the treatment period versus the pretreatment period. Secondary outcome measures included acute-phase reactant levels, health-related quality of life (Child Health Questionnaire—Parent Form 50 [CHO-PF50]) (5), physician’s global assessment of FMF control, time to attack following the last canakinumab injection (day 57), and safety and tolerability of canakinumab.

Six participants met the primary outcome measure with a ≥50% reduction (range 76–100%) in the rate of FMF attacks (Figure 1). The median 28-day time-adjusted attack rate decreased from 2.7 to 0.3 (89%). Three participants did not experience any attacks during the treatment phase. The canakinumab dose was doubled for the second and third injections in 2 participants: a responder who experienced 1 additional brief attack after dose escalation and the single nonresponder, who experienced 3 additional attacks (4 attacks overall). Compared with 34 attacks over 374 patient-days of followup during the pretreatment phase, only 8 attacks in 601 patient-days were reported during the treatment phase. The proportion of days that participants were experiencing an attack decreased from 24.2% to 3.6%. Eighteen of 34 attacks (53%) were rated as severe or very severe during the pretreatment phase, compared with 0 of 8 during the treatment phase. Following the first injection, clinical manifestations resolved the same day in 4 participants and within 24 hours in 3. Five participants developed an attack after the last canakinumab injection, within a median of 25 days (range 5–34).

Median C-reactive protein levels normalized by day 8 (from 74 mg/liter at baseline to 2 mg/liter on day 8 and 1.3 mg/liter on day 86), the erythrocyte sedimentation rate by day 29 (from 83 mm/hour at baseline to 17 mm/hour on days 29 and 86), and serum amyloid A levels by day 57 (from >500 mg/liter at baseline to 2.5 mg/liter on day 57 and 12.2 mg/liter on day 86). Health-related quality of life also improved, with an increase in CHO-PF50 summary scores for both the physical domain (from a median of 21 at baseline to 46 on day 86 [mean 50 in the healthy population]) and the psychosocial domain (31 to 40). The physician’s global assessment of FMF control at baseline was rated as very poor in 3 participants, poor in 3, and fair in 1. By day 86 this had improved to very good in 4 participants and good in 3.

Eleven adverse events (AEs) were reported in 4 participants: 2 were infections. All were mild except for 1 moderate streptococcal throat infection. There were no serious AEs, opportunistic infections, malignancies, or deaths. No significant laboratory abnormalities occurred, and formation of neutralizing antibodies to canakinumab was not observed. No participants discontinued the study or missed a treatment dose because of an AE.

The major limitation of this study, which was primarily a proof-of-concept study, was the small sample size. Of note, the proportion of complete responders (with no attacks) was lower than has been reported in studies of other autoinflammatory conditions treated with canakinumab, such as cryopyrin-associated periodic syndrome (6) and tumor necrosis factor receptor–associated periodic syndrome (7), but higher than has been reported in systemic juvenile idiopathic arthritis (8). This may be due in part to the selection, for the present study, of patients whose FMF was severe and resistant to colchicine treatment. The proportion of complete responders was slightly greater in this study than in a randomized trial of rilonacept treatment in a similar FMF population (3).
In summary, canakinumab was shown to be effective in treating pediatric patients with colchicine-resistant familial Mediterranean fever treated with canakinumab. Dose escalation was required in order to prevent attacks in some children. AEs were minor and manageable. All participants continued to receive canakinumab after the trial ended. A larger controlled study is needed to better evaluate the benefit of canakinumab in this population, including the optimal dose and interval of treatment, taking into account the high cost of IL-1 inhibitors.

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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. Dr. Hashkes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brik, Butbul-Aviel, Ben Dayan, Tseng, Hashkes.

Acquisition of data. Brik, Butbul-Aviel, Lubin, Ben Dayan, Rachmilewitz-Minei, Hashkes.


ROLE OF THE STUDY SPONSOR

Novartis facilitated the study design, helped with the data analysis, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Novartis.

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Long-term efficacy and safety of Canakinumab in active Hyper-IgD syndrome (HIDS): results from an open-label study

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From 8th International Congress of Familial Mediterranean Fever and Systemic Autoinflammatory Diseases Dresden, Germany. 30 September - 3 October 2015

Introduction
Hyper-IgD with periodic fever syndrome (HIDS) is an autoinflammatory disease characterized by periodic episodes of fever, abdominal distress, joint pain, and skin rashes. IL-1 blockade was previously reported as effective in reducing the frequency of episodes and improving clinical symptoms.[1,2] We report the results of the study assessing the efficacy and safety of canakinumab, an anti-IL-1β human monoclonal antibody, in patients with active HIDS.

Objectives
The primary objective was to assess the reduction of frequency of flares during the 6-month treatment period compared to a historical period (HP). Secondarily, assessments of reduction in frequency of flares during 24-month long-term follow-up and adverse events (AE) were conducted.

Patients and methods
This was an open-label, single treatment arm study to assess the efficacy and safety of canakinumab in HIDS patients aged ≥2 years with biallelic MVK mutations. The study included a 6-month treatment period (6TP) with up to 6-month withdrawal period (WP) and 24-month long-term treatment period (24TP).

Results
All enrolled patients (n=9) completed the 6TP and the WP, with 8 completing the 24TP. The median number of flares decreased from 5 (3-12) during HP to 0 (0-2) during 6TP. The median remained at 0 (0-3) until the end of study. During the 24TP, the median flare duration was 3.5 days (2-8, first year) and 8.5 days (6-11, second year). Flare severity remained ‘mild’ to ‘moderate’ at baseline and decreased to ‘mild’ or ‘minimal’ signs/symptoms and to ‘mild’ or without signs/symptoms” at the first and second year of the 24TP, respectively. Physician’s global assessment scores for HIDS disease control changed from either ‘no control’ or ‘poor control’ at baseline to ‘good’ or ‘excellent control’ by Day 4 and were maintained until the end of study. CRP and SAA plasma levels normalized by Day 15 and remained normal thereafter. The most frequent AEs were infections, with four patients experienced 14 mild to moderate SAEs. No AEs were drug-related nor led to discontinuation of study treatment.

Conclusions
Canakinumab markedly reduced the frequency of flares, rapidly alleviated signs and symptoms of acute episodes and normalized the serological inflammatory markers. The safety profile is consistent with other canakinumab studies. These data support a safe and maintained disease control and reinforce the ongoing development of canakinumab in this therapeutic area.

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EXTENDED REPORT

Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study

Marco Gattorno, Laura Obici, Marco Cattalini, Vincent Tormey, Ken Abrams, Nicole Davis, Antonio Speziale, Suraj G Bhansali, Alberto Martini, Helen J Lachmann

ABSTRACT

Objective To evaluate the efficacy of canakinumab, a high-affinity human monoclonal anti-interleukin-1β antibody, in inducing complete or almost complete responses in patients with active tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

Methods Twenty patients (aged 7–78 years) with active recurrent or chronic TRAPS were treated with canakinumab 150 mg every 4 weeks for 4 months (2 mg/kg for those ≤40 kg) in this open-label, proof-of-concept, phase II study. Canakinumab was then withdrawn for up to 5 months, with reintroduction on relapse, and 4 weekly administration (subsequently increased to every 8 weeks) for 24 months. The primary efficacy variable was the proportion of patients achieving complete or almost complete response at day 15, defined as clinical remission (Physician’s Global Assessment score ≤1) and full or partial serological remission.

Results Nineteen patients (19/20, 95%; 95% CI 75.1% to 99.9%) achieved the primary efficacy variable. Responses to canakinumab occurred rapidly; median time to clinical remission 4 days (95% CI 3 to 8 days). All patients relapsed after canakinumab was withdrawn; median time to relapse 91.5 days (95% CI 65 to 117 days). On reintroduction of canakinumab, clinical and serological responses were similar to those seen during the first phase, and were sustained throughout treatment. Canakinumab was well tolerated and clinical responses were accompanied by rapid and sustained improvement in health-related quality of life. Weight normalised pharmacokinetics of canakinumab, although limited, appeared to be consistent with historical canakinumab data.

Conclusions Canakinumab induces rapid disease control in patients with active TRAPS, and clinical benefits are sustained during long-term treatment.

Trial registration number NCT01242813; Results.

INTRODUCTION

Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant autoinflammatory disorder resulting from variants in the TNF super family receptor 1A (TNFRSF1A) gene. Clinically, TRAPS is characterised by recurrent fever, myalgia, abdominal pain, rash, headaches, ocular symptoms and in some cases, amyloid A (AA) amyloidosis. Diagnosis is challenging due to the considerable genetic heterogeneity and variable clinical presentation.

Non-steroidal anti-inflammatory drugs (NSAIDs) can relieve fever but have little other benefit in TRAPS, and conventional immunomodulators are ineffective. Biologics that target specific proinflammatory cytokines have been investigated as treatment for TRAPS. At the time of the identification of the molecular defect, the TNF inhibitor etanercept was the cornerstone of TRAPS therapy; it attenuates symptoms and inflammatory markers but many patients discontinue therapy due to perceived lack of efficacy. Paradoxically, treatment with the TNF inhibitors infliximab and adalimumab can precipitate inflammatory attacks and disease worsening.

TNFRSF1A gene mutations in TRAPS are thought to cause aberrant trafficking and localisation of the type I TNF receptor, resulting in intracellular stress ultimately leading to increased production of interleukin-1β (IL-1β). While the pathogenesis of TRAPS is complex and still not completely understood, patients with TRAPS have excellent short-term response to the IL-1 receptor antagonist anakinra, suggesting IL-1β as a rational therapeutic target.

Canakinumab is a high-affinity human monoclonal IL-1β antibody of the IgG1/κ isotype that binds to IL-1β, thereby blocking the interaction of the cytokine with its receptor. Case studies have demonstrated that patients with TRAPS can achieve a complete or near complete response with canakinumab treatment. This phase II proof-of-concept study was designed to evaluate the efficacy and safety of canakinumab in inducing complete or almost complete responses within 15 days after the first dose in patients with active TRAPS.

METHODS

Study design This open-label, single-treatment arm, proof-of-concept, phase II study was conducted at six centres (four in Italy, one in England and one in Ireland) from 2010 to 2014. The study was registered at ClinicalTrials.gov (NCT01242813), and was conducted according to the ethical principles from the Declaration of Helsinki and in compliance with...
Good Clinical Practice. An independent ethics committee at each site approved the protocol.

The study enrolled patients with a clinical diagnosis of active recurrent or chronic TRAPS with a confirmed mutation of the TNFRSF1A gene (see online supplement for eligibility criteria), and consisted of a 4-month treatment period, followed by a withdrawal/follow-up period lasting up to 5 months, and, on disease relapse, a 24-month long-term treatment period (see online supplementary figure S1). Patients weighing >40 kg received canakinumab 150 mg subcutaneously once every four weeks during the treatment period (days 1, 29, 57 and 85). A single-dose up-titration to 300 mg was permitted at day 8 in non-responders at the discretion of the treating physician. Patients weighing ≤40 kg received canakinumab 2 mg/kg once every four weeks, with a single-dose up-titration to 4 mg/kg allowed for non-responders at day 8. Patients who relapsed during the follow-up period received another dose of canakinumab equivalent to the last dose received, and then returned 2 weeks later for the end of follow-up visit. All patients who completed or relapsed during the follow-up period entered the long-term treatment period. In patients with a stable complete response, corticosteroid doses could be reduced at the investigators discretion from day 29 for complete responders only. The once every four weeks dosing regimen was chosen in the absence of sufficient clinical pharmacokinetic/pharmacodynamic data in patients with TRAPS. However, in the long-term treatment period, based on obtained pharmacokinetic/pharmacodynamic data, patients were transitioned to a dosing interval of once every eight weeks.

**Efficacy, pharmacokinetic and safety assessments**

Patients had visits on days 1 (baseline), 3, 8, 15, 29, 57 and 85, and then every 4 weeks during follow-up and long-term treatment. At each visit, investigators completed a global assessment using a 5-point Physician’s Global Assessment (PGA) scale with scores of 0 (none), 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe) for TRAPS-associated clinical signs and symptoms. The PGA was developed based upon discussions with the principal investigators and in accordance with the same instrument used previously in canakinumab trials in CAPS; the PGA was not validated for use in TRAPS. Investigators also rated the severity of four-key associated signs and symptoms (rash, extremity musculoskeletal pain, abdominal pain and eye manifestations) using a 5-point scale with scores of 0 (absent), 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe). Fever (>38.5°C) was also assessed at all visits. The inflammatory markers C-reactive protein (CRP) and serum amyloid A (SAA) were measured at each visit; CRP levels were determined locally and standardised to a normal range of 0–10 mg/L, and SAA levels were determined at the central laboratory.

The primary efficacy variable was the proportion of patients with active TRAPS achieving complete or almost complete response at day 15. Complete response was defined as clinical remission (PGA score ≤1) with full serological remission (CRP <10 mg/L and/or SAA <10 mg/L), and almost complete response was defined as clinical remission with partial serological remission (≥70% reduction of baseline CRP and/or SAA). Non-response was defined as no change or worsening from baseline PGA score and/or increased or <50% reduction from baseline CRP and/or SAA. Clinical relapse was defined by an increase in PGA score of ≥1 point from day 15 to a PGA score ≥2, and serological relapse was defined by an increase in CRP and/or SAA by 30% from day 15 to a value ≥30 mg/L unless it resulted from other factors (eg, concurrent infection).

Secondary efficacy variables included the proportion of patients with complete or almost complete response at day 8, the proportion with clinical remission at days 8 and 15, the proportion with serological remission at days 8 and 15, the time to the investigator’s assessment of clinical remission, and the time to relapse in the withdrawal phase. The designation of almost complete response was made to identify patients with evident amelioration of disease activity, and functionally served to select patients who did not need re-dosing with canakinumab.

Pharmacokinetic and safety assessments are described in the online supplement.

**Health-related quality of life**

Exploratory objectives included an assessment of long-term maintenance of disability and health-related quality of life (HRQoL) of canakinumab treatment in patients with TRAPS. Patients completed HRQoL questionnaires on days 1, 15, 113, and then every 12 weeks during long-term treatment. Patients ≥18 years of age at baseline completed the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), and those <18 years completed the Child Health Questionnaire (CHQ-PF50). Neither of these tools has been validated for use in TRAPS.

**RESULTS**

**Patients**

Twenty patients were treated with canakinumab and all entered the long-term treatment period. Eighteen patients completed the long-term treatment period. Two patients were lost to follow-up after receiving treatment to days 673 and 692, respectively. The mean age of the study cohort was 34.6 years; 95% were white and 63% were male (table 1). Six patients were <18 years of age (paediatric) and 14 patients were ≥18 years of age (adult). The mean duration of time since TRAPS diagnosis at entry was 4.6 years. Nine patients had recurrent TRAPS, with a mean of 9.9±2.32 episodes per year and episodes lasting for a mean of 11.9±3.76 days. The remaining 11 patients had chronic TRAPS, with continuous symptoms or persistent elevation of acute phase reactants; one of those patients required continuous steroid treatment. Three patients (15%) had AA amyloidosis, one of these also had a medical history of bronchiectasis and retroperitoneal fibrosis. Overall, 19 patients (95%) received prior TRAPS treatment (table 1), which was discontinued per the protocol. Canakinumab was initiated when patients met criteria for active TRAPS but before they developed a severe disease flare.

**Efficacy**

The primary efficacy endpoint of complete or almost complete response at day 15 was achieved by 19 of 20 patients (95%; 95% CI 75.1% to 99.9%). The other patient had achieved a complete response at day 8, but lost the serological response at day 15 despite ongoing clinical remission. Overall, 16 patients (80%) achieved a complete response at day 8, and 2 additional patients (n=18; 90%) experienced complete clinical remission (ie, PGA score ≤1) at day 8 despite not yet achieving a serological response (figure 1). All patients remained in clinical remission during the 4-month treatment period except for one patient who had a PGA assessment of mild TRAPS activity at the day 85 dosing visit. The median time to clinical remission was 4 days (95% CI 3 to 8 days) (see online supplementary figure S2). Canakinumab improved each of the key signs and symptoms of TRAPS (see online supplementary table S1). The
six paediatric patients responded similarly to the adults, with all achieving a complete or almost complete response at day 15.

The inflammatory biomarkers CRP and SAA decreased rapidly after initiation of canakinumab treatment. Both CRP and SAA were within normal ranges (≤10 mg/L) in seven patients (35%) on day 8 and in 12 patients (60%) on day 15. For the study cohort, median CRP and SAA declined to ≤10 mg/L by day 15 and remained within a normal range for the duration of the treatment period (figure 2). Median CRP and SAA values were 4.8 and 2.2 mg/L, respectively, at the end of the treatment period, and remained within the normal range throughout the long-term treatment period (see online supplementary table S2).

Up-titration was allowed for patients who did not achieve a complete or almost complete response at day 8. Two of the four non-responders at day 8 were up-titrated and achieved a complete or almost complete response by day 15. Despite not receiving up-titration the other two patients still achieved a complete or almost complete response at day 15.

All 20 patients relapsed (11 mild, 7 moderate and 2 severe) during the canakinumab withdrawal/follow-up period. Based on Kaplan-Meier estimates, the median time to relapse following the last canakinumab dose was 91.5 days (95% CI 65 to 117 days) (see online supplementary figure S3). At 2 weeks after re-starting canakinumab following relapse, all patients returned to the level of response they had achieved prior to stopping canakinumab.

Based on analysis of time to relapse, the pharmacokinetic data obtained, and the desire of both patients and physicians to decrease the dose frequency, all patients in the long-term treatment period transitioned to a maintenance dosing interval of once every eight weeks of the last dose they received on day 85 (ie, 150 or 300 mg (or 2 or 4 mg/kg, respectively, if <40 kg)). For seven patients (35%; six adults, one child), the decreased dosing frequency at the lower 150-mg dose was not adequate to maintain disease control: three patients experienced one relapse episode, three patients experienced two relapse episodes and one patient experienced five relapse episodes. Four patients received NSAIDs and one patient received corticosteroid

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**Table 1** Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study cohort (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean (SD) 34.6 (18.36)</td>
</tr>
<tr>
<td>Range</td>
<td>7.0–77.8</td>
</tr>
<tr>
<td>Age range, years</td>
<td>&lt;18 6 (30) ≥18 14 (70)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 13 (65) Female 7 (35)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White 19 (95) Asian 1 (5)</td>
</tr>
<tr>
<td>Duration since TRAPS diagnosis, years</td>
<td>Mean (SD) 4.6 (3.57) Range 0.01–11.7</td>
</tr>
<tr>
<td>Diagnosis of TRAPS, n (%)</td>
<td>Chronic 11 (55) Relapsing 9 (45)</td>
</tr>
<tr>
<td>Number of episodes/year: mean (SD)</td>
<td>9.9 (2.32) Duration of each episode, days: mean (SD) 11.9 (3.76)</td>
</tr>
<tr>
<td>CRP, mg/L: median (range)</td>
<td>125 (6–564) SAA, mg/L: median (range) 198 (16–2270) PGA of TRAPS activity, n (%) 2 (mild) 13 (65) 3 (moderate) 6 (30) 4 (severe) 1 (5)</td>
</tr>
<tr>
<td>Disease-related medication taken before but stopped prior to study entry,* n (%)</td>
<td>IL-1 inhibitor (anakinra) 13 (65)† TNF inhibitor (etanercept) 6 (30)‡ Glucocorticoids 10 (50)§ NSAIDs 3 (15)%</td>
</tr>
</tbody>
</table>

---

*As per study protocol. †CR, n=12; PR, n=1. ‡CR, n=3; PR, n=3. §CR, n=6; PR, n=2; other, n=2 (treatment of TRAPS attack, prophylaxis). ¶PR, n=3. CR, complete response; CRP, C-reactive protein (standardised); IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PGA, Physician’s Global Assessment; PR, partial response; SAA, serum amyloid A; TNF, tumour necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.
treatment to manage these acute relapses. The dose of canakinumab was up-titrated to 300 mg once every eight weeks in five of these patients, while the dose was not up-titrated in the remaining two patients, as they had isolated relapses not deemed severe or frequent enough by their treating physician to warrant a dose escalation.

Health-related quality of life
At baseline, 16 patients completed the SF-36 at least once. The patients exhibited considerable deficits in HRQoL compared with age and gender matched norms across all SF-36 domains; the mean differences on all domains exceeded the minimal clinically important difference of each scale and were statistically significant (*p*<0.05). The greatest deficits in terms of effect sizes between patients with TRAPS and the general US population were observed for the role emotional, general health and bodily pain domains (figure 3A). When compared with benchmark samples of patients with other diseases, the HRQoL of the patients with TRAPS was most closely matched to patients with rheumatoid arthritis. Domain and summary SF-36 scores for the patients with TRAPS were consistently below those for patients with osteoarthritis or chronic back problems.

Treatment with canakinumab rapidly improved HRQoL in parallel with clinical improvement (figure 3B). Scores on all SF-36 domains increased from baseline to day 15 (n=14), with mean scores >50 (general population average) on the physical functioning and vitality domains. By the end of treatment period on day 113 (n=15), all domain scores were >50 except for general health and role emotional. The mean physical component summary score improved from 41.8 at baseline to 49.3 at day 15 and 51.4 at day 113; the mean mental component summary score showed improvements from 39.3 at baseline to 46.6 at day 15 and 49.0 at day 113. For the five paediatric patients who completed the CHQ-PF50 questionnaire, the mean physical health and psychosocial scores at baseline were 35.4 and 52.7, respectively. Improvements in mean physical health scores to >40 were evident by day 15 and were maintained at the end of treatment and end of follow-up visits. Mean psychosocial scores remained >50 throughout the study, except on days 365 and 617, they were noted at 46.6 and 47.2, respectively.

Pharmacokinetic profile
In general, canakinumab displayed pharmacokinetic properties typical of an IgG1 monoclonal antibody. The pharmacokinetics of canakinumab in this population were consistent with that observed in other disease populations (see online supplementary table S3).

Safety
Canakinumab treatment was well tolerated; all patients reported at least one adverse event (AE), most commonly nasopharyngitis, abdominal pain, headache and oropharyngeal pain (table 2). Most AEs were mild to moderate in severity, and none led to study discontinuation. Serious adverse events, including pericarditis, abdominal pain, diarrhoea, intestinal obstruction, vomiting, upper respiratory tract infection, meniscus injury, hypertriglyceridaemia, hyperkalemia, pregnancy-related condition (ie, wife of enrolled patient became pregnant), foot deformity and condition aggravated occurred in seven patients. None of these events were suspected as drug-related (see online supplementary table S4). There were no meaningful changes in haematology, clinical chemistry or vital signs during the study, and no neutralising anti-canakinumab antibodies were identified.

DISCUSSION
Canakinumab treatment produced rapid clinical and serological responses in paediatric and adult patients with active TRAPS. All patients achieved clinical remission in a median of 4 days after the first canakinumab dose. Importantly, both

![Figure 2](http://ard.bmj.com/) Median C-reactive protein (CRP) and serum amyloid A (SAA) values during the 4-month treatment period in the study cohort. BL, baseline; ULN, upper limit of normal.

![Figure 3](http://ard.bmj.com/)

**Figure 3** SF-36 spydergrams. (A) Comparison of tumour necrosis factor receptor-associated periodic syndrome (TRAPS) cohort with age and gender matched US population norm. (B) Effect of canakinumab at day 15 (primary endpoint) and day 113 (end of treatment period) compared with baseline.
The remarkable clinical and serological response was paralleled by a similarly rapid and robust improvement in HRQoL. Responses were sustained with continued canakinumab dosing; relapse occurred in all patients after withdrawal of canakinumab, but responses were restored after restarting canakinumab treatment.

This study corroborates findings from previous anecdotal reports in which the IL-1 receptor antagonists anakinra and canakinumab were used in the treatment of patients with refractory TRAPS, and support the key role of IL-1β rather than TNF in the pathogenesis of TRAPS. Clinically, TNF inhibition with etanercept, has proved disappointing in TRAPS. In the only prospective, open-label study, the benefit of etanercept was not sustained over time and 8 of 14 patients discontinued etanercept in the first 2 years, mainly due to lack of efficacy.5

Prior to our study, 65% of the patients had been treated successfully with the IL-1 receptor antagonist anakinra, and after a brief washout period, all responded to canakinumab, further supporting the long-term efficacy of IL-1 inhibition compared with TNF inhibition in patients with TRAPS.7

For the long-term period, patients were transitioned from canakinumab once every four weeks to once every eight weeks, the same dosing interval indicated for patients with another hereditary fever syndrome, cryopyrin-associated periodic syndromes. However, because maintenance canakinumab at 150 mg once every eight weeks led to relapses in a significant minority (33%) of patients, a 150-mg once every four weeks regimen has been adopted for the ongoing pivotal phase III clinical trial (clinicaltrials.gov NCT02059291) evaluating efficacy and safety of canakinumab versus placebo in patients with hereditary periodic fever syndromes (TRAPS, familial Mediterranean fever and hyperimmunoglobulin D syndrome/mevalonate kinase deficiency).2,22

At baseline, patients with TRAPS showed a clinically meaningful and statistically significant decrement in HRQoL compared with age and gender matched US population norms. Mean physical and mental component summary scores as well as 5 domain scores in the TRAPS cohort were 10 points below those for the US population (ie, 2 SDs lower). Notably, treatment with canakinumab rapidly improved HRQoL, with SF-36 component and domain scores approaching or reaching those for the normal US population.

In general, canakinumab displayed pharmacokinetic properties typical of an IgG1 monoclonal antibody with findings in this population consistent with that observed in other disease populations.

The benign safety profile observed in this small study was consistent with that observed in larger blinded trials of canakinumab in other conditions, including CAPS and systemic idiopathic juvenile arthritis. The oldest patient treated in this study was 77 years old with comorbidities, and she has been treated successfully for several years without serious adverse events.

In summary, this study demonstrates that canakinumab produces rapid and robust clinical and serological responses, with parallel improvements in HRQoL, in patients with active TRAPS. This study supports continued exploration of the use of canakinumab in the treatment of TRAPS.

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### Funding

This study was sponsored and funded by Novartis.

### Competing interests

KA: employee of Novartis Pharmaceuticals Corporation. SB: employee of Novartis Pharmaceuticals Corporation. MC: received speaker fees and served as a consultant for Novartis and SOBI. ND: employee of Novartis Pharmaceuticals Corporation. MG: received speaker fees and served as a consultant for Novartis and SOBI, and has received unrestricted grants for the Eurofever Registry from Novartis and SOBI. HL: received speaker fees and served as a consultant for Novartis and SOBI. AM: received speaker fees and served as a consultant for Novartis. LD: received speaker fees and served as a consultant for Novartis. AS: employee of Novartis Pharma AG.

### Table 2 Adverse events occurring in at least 3 patients by preferred term during the entire study (study duration: 33 months)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Study cohort (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Cough</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Condition aggravated</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Chest pain*</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Ear pain</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Tootache</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

*Of these three events, two were non-cardiac chest pain and the other was related to tumour necrosis factor receptor-associated periodic syndrome (TRAPS) disease activity.

None were considered related to canakinumab by the investigator.
Clinical and epidemiological research

Ethics approval The study was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were reviewed by the independent ethics committee (IEC) or institutional review board (IRB) for each centre: Clinical Research Ethics Committee, Merlin Park Hospital, Galway, Ireland; National Research Ethics Service, Southampton & South West Hampshire REC(B), Berkshire, UK; Comitato Di Bioetica Dell’ IRCCS Istituto Giannina Gaslini Di Genova, Genova, Italy; Comitato Di Bioetica Della Fondazione IRCCS Policlinico San Matteo Di Pavia, Pavia, Italy; Comitato Etico Azienda ospedaliera Spedali Civili Di Brescia, Brescia, Italy; Comitato Etico Dell’ASL 1 Di Agrigento, Agrigento, Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

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Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study

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Efficacy and Safety of Canakinumab in Patients with Colchicine-Resistant Familial Mediterranean Fever, Hyper-Immunoglobulin D Syndrome/Mevalonate Kinase Deficiency and TNF Receptor-Associated Periodic Syndrome: 40 Week Results from the Pivotal Phase 3 Umbrella Cluster Trial

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SESSION INFORMATION
Session Date: Sunday, November 13, 2016
Session Title: ACR Late-Breaking Poster Session
Session Type: ACR Late-breaking Abstract Session
Session Time: 9:00AM-11:00AM

Background/Purpose: Evidence points to the role of abnormal IL-1β production in familial Mediterranean fever (FMF), hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and TNF receptor-associated periodic syndrome (TRAPS). Analysis of the efficacy of canakinumab (CAN), a fully human anti-IL-1β monoclonal antibody, in the double-blind randomized epoch 2 of the phase 3 CLUSTER trial in patients (pts) with colchicine-resistant FMF (crFMF), HIDS/MKD or TRAPS has demonstrated highly significant differences vs placebo (PBO) in the primary outcome (resolution of the index flare by Day 15 and no subsequent flares up to week [wk] 16) in the 3 diseases. Here we report the results from the subsequent epoch 3 (up to wk 40) that included a randomized withdrawal phase to evaluate CAN at a prolonged dosing interval (8 wks [q8w]) or complete discontinuation.

Methods: The study comprises 3 disease cohorts (crFMF, HIDS/MKD and TRAPS) and 4 epochs: a 12-wk screening epoch (E1), a 16-wk randomized treatment epoch (E2), a 24-wk randomized withdrawal epoch (E3) and a 72-wk open-label treatment epoch (E4). Pts who were initially randomized to CAN 150 mg every 4 wks (q4w) and did not flare in E2 were re-randomized 1:1 to CAN 150 mg q8w or PBO in E3. The endpoint of E3 was the proportion of pts who maintained control of disease (no flares: PGA ≤2 and CRP ≤30 mg/L) between Wk 16 and Wk 40 after re-randomization to CAN 150 mg q8w vs PBO. Moreover, in order to gain additional information on the maintenance dose in the long-term, pts who escaped to open-label CAN during E2, were dosed to open-label CAN 150 mg q8w during E3. Pts with a flare could be escalated up to 300 mg q4w.

Results: 42 pts who were CAN (150 mg q4w) responders in E2 were re-randomized to CAN 150 mg q8w or PBO in E3. At Wk 40, the proportion of responders was numerically higher in the CAN vs PBO group in all 3 disease cohorts (Table). Overall in E3, including pts treated in open-label, 49% of the crFMF pts, 53% of the TRAPS pts and 23% of the HIDS/MKD pts maintained disease control with a prolonged dosing interval (150 mg q8w). Up-titration to 300 mg q4w was needed in few pts with crFMF (10%) or TRAPS (8%) and in 29% of those with HIDS/MKD. No new safety findings were reported in CAN-treated pts through E3, with no toxicity accumulation (Table). No deaths were reported in the 3 disease cohorts.

Conclusion: The results of E3 in this pivotal trial confirm long-term efficacy of CAN in crFMF, HIDS/MKD and TRAPS, and yield information on the long-term dose needed to control disease, with approximately half of the pts with crFMF or TRAPS and approximately 1/3 of the pts with HIDS/MKD showing no flare at a prolonged dose interval administration of 150 mg q8w. The higher dose of 300 mg q4w was needed in few pts with crFMF or TRAPS and in 1/3 of the pts with HIDS/MKD. No new safety issues were reported over 40 wks of CAN treatment; the safety profile was not distinct from previous controlled studies.

<table>
<thead>
<tr>
<th>Table. Efficacy results up to 40 weeks and summary of safety</th>
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<tr>
<td><strong>Efficacy</strong></td>
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<tr>
<td>Proportion of responders, r/100 (%)</td>
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<tr>
<td></td>
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<tr>
<td>Cohort</td>
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<td>CAN (150 mg q8w)</td>
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<tr>
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<tr>
<th>Safety</th>
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<td>Exposure to canakinumab (PV)</td>
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*Any patient who received a dose of CAN during epoch 2 or 3.


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