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Clinical evidence review of canakinumab for treating periodic fever syndromes (tumour necrosis factor receptor associated periodic syndrome [TRAPS], hyperimmunoglobulin D syndrome/mevalonate kinase deficiency [HIDS/MKD] and familial Mediterranean fever [FMF])

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About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers canakinumab for treating the following periodic fever syndromes; tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and familial Mediterranean fever (FMF) in adults and children aged 2 years and older. Canakinumab is also licensed for the treatment of another type of periodic fever syndrome, cryopyrin-associated periodic syndromes (CAPS) which is outside the scope of this evidence review.

Periodic fever syndromes may be caused by a variety of different genetic defects. The underlying gene defects can cause abnormal activation of the immune system leading to dysregulation of cytokines (such as interleukin-1 beta) and excessive inflammation (European public assessment report [EPAR] for canakinumab). There is overlap in the clinical features of TRAPS, HIDS/MKD and FMF. These include recurrent episodes of systemic inflammation accompanied by fever and characteristic symptoms and signs in target organs and body systems. Fever episodes last from days to months depending on the condition.

The evidence review primarily considers the results of 1 randomised controlled trial (RCT) (De Benedetti.et al. 2018) that was the pivotal study that compared canakinumab with placebo in people with TRAPS (n=46), MKD (n=72) and colchicine-resistant FMF (cr-FMF, n=63) in separate groups. The pivotal study was split into 4 parts that included a 16-week randomised treatment phase and a 24-week randomised withdrawal and open-label treatment phase. This CER also considers 4 phase 2 open-label single-arm studies, Arostegui et al. 2017 (n=9 with HIDS), Brik et al.2014 (n=7 with cr-FMF), Gattorno et al. 2017 (n=20 with TRAPS) and Gul et al. 2015 (n=9 with cr-FMF) that all measured efficacy of canakinumab relative to baseline values. In addition, 1 unpublished paper (Lachmann et al. in press) provided health-related quality of life results from the pivotal study by De Benedetti et al. 2018. The data from the unpublished study is academic-in-confidence (AIC) data and is underlined and highlighted in yellow throughout the evidence review.

Effectiveness

Evidence from the pivotal study suggests that significantly more people with TRAPS, MKD and cr-FMF reported complete response with canakinumab compared with placebo (45% versus 8%, odds ratio [OR] 9.17 [95% confidence interval [CI] 1.51 to 94.6] p=0.006, 35% versus 6%. OR 8.94 [95% CI 1.72 to 86.4] p=0.003 and 61% versus 6%, OR 23.8 [95% CI 4.38 to 227.5] p<0.001, respectively) at week 16 of the randomised treatment period. The pivotal study also found that in participants with TRAPS, MKD and cr-FMF who did not have a complete response at week 16, the mean number of flares decreased from baseline (10.2, 14.7 and 32.5 per year respectively) to week 40 (normalised to 1 year, 1.2, 2 and 1.2 per year respectively).

In the pivotal study, more participants with TRAPS, MKD and cr-FMF were found to have better control of their condition (measured by the physician's global assessment score [PGA]) and a reduction in inflammation (measured using C-reactive protein [CRP] and serum amyloid A [SAA]) with canakinumab compared with placebo. By reducing the SAA level, the risk of developing kidney failure is reduced which is an important finding for people with the condition.

[redacted]

In summary, the studies suggest that canakinumab may resolve flares (or 'attacks'), reduce the number and intensity of flares, reduce inflammation and improve disease control and [redacted] in people with TRAPS, HIDS/MKD and cr-FMF. When interpreting these results, the evidence gaps and limitations (see below) should also be taken in to account.

Safety and tolerability

No deaths, opportunistic infections or cancers were reported in any of the included studies.

Adverse events and serious adverse events were higher with canakinumab compared with placebo (497 versus 136 and 21 versus 8, respectively) during the randomised treatment period of 16 weeks, although people in the canakinumab

group had a longer exposure to treatment (12.1, 19.1 and 16.4 patient-years, respectively) compared with the combined placebo group (8 patient-years). The most frequently reported adverse events were infections (particularly respiratory infections), abdominal pain, headaches, and injection-site reactions with 12 being considered serious and had resolved. Additionally, the EPAR states that "the adverse event profile of canakinumab treatment is overall mostly comparable in the new proposed indication [for TRAPS, FMF and HID/MKD] with the approved CAPS indication."

The SPC states that canakinumab is associated with an increased incidence of serious infections and that people receiving treatment should be monitored carefully for signs and symptoms of infections during and after treatment. Caution should be exercised when treating people with infections, a history of recurring infections or underlying conditions that may predispose them to infections. The summary of product characteristics for canakinumab states that more than 2,600 people have been treated with canakinumab, including children, healthy volunteers and people in interventional studies with CAPS, TRAPS, HIDS/MKD, FMF, systemic juvenile idiopathic arthritis, gouty arthritis or other interleukin-1 beta mediated diseases.

Evidence gaps and limitations

Canakinumab treatment was studied in adults and children aged 2 years and older. No data are available for people with renal or hepatic impairment and there are limited data on using canakinumab in pregnant women. There are limited data for people with FMF who have no prior use of colchicine.

The EPAR states that the primary and secondary outcomes of the pivotal study were more robust than those used in the phase 2 studies and are adequate to demonstrate a clinically relevant treatment response. Main limitations of the studies included the number of participants with TRAPS, HIDS/MKD and cr-FMF in the studies was small because of the conditions being rare. Most of the participants with cr-FMF in the studies took colchicine alongside canakinumab which may confound the results in this population. Most of the studies were of a short duration and so long-term efficacy and safety data are limited in people with TRAPS, HIDS/MKD and FMF. [redacted]

[redacted].

Also, there were no data reporting outcomes that were considered to be important such as effect on growth, work or school attendance, fertility, long-term complications (such as amyloid A amyloidosis) and burden of medicines to manage associated symptoms. There were no other comparators such as biologics in any of the included studies to assess where canakinumab is best placed in the treatment pathway for TRAPS, HIDS/MKD and FMF.

The design of the 4 supporting phase 2 open-label studies' means they are subject to bias and confounding, are difficult to interpret, and cannot support firm conclusions. However, it is important to note that placebo arms are limited for ethical reasons when conducting clinical trials in severe diseases such as periodic fever syndromes.

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Abbreviations

Term	Definition
CHQ-PF50	Child health questionnaire-parent form 50
cr-FMF	Colchicine-resistant familial Mediterranean fever
CRP	C-reactive protein
HIDS/MKD	Hyperimmunoglobulin D syndrome/ mevalonate kinase deficiency
FMF	Familial Mediterranean fever
NSAIDs	Non-steroidal anti-inflammatory drugs
SAA	Serum amyloid A
TNF	Tumour necrosis factor
TRAPS	Tumour necrosis factor receptor associated periodic syndrome

Medical definitions

Term	Definition
Amyloidosis	A condition in which an abnormal protein called amyloid builds up in tissues and organs
Autosomal dominant inheritance	1 gene that is mutated and is inherited from either parent causing a genetic disorder
Autosomal recessive inheritance	2 genes that have mutated are inherited, with 1 coming from each parent, causing a genetic disorder
Biologics	Medicines that are monoclonal antibodies for example canakinumab
Colchicine	Colchicine is a medicine that modulates white cell function, and is used as preventative treatment in most people with FMF and sometimes in other periodic fever conditions. Its effectiveness may reduce over time and it may cause intolerable adverse effects such as diarrhoea
Colchicine-resistant- familial Mediterranean fever	People with FMF who have an incomplete response to adequate colchicine doses
Corticosteroids	Also known as steroids and are anti-inflammatory medicines used to treat a range of conditions. There are 2 main classes, glucocorticoids (see below) and mineralocorticoids
C-reactive protein	A type of protein that is raised in response to inflammation

Cytokines	A type of protein produced by cells that have a part to play in the immune system. There are different cytokines based on either the type of cell that makes them or the action they have in the body (for example interleukin 1 is made by leukocytes [type of white blood cell] that acts on other leukocytes). Excess amounts of cytokines can cause inflammation and tissue destruction
Erythrocyte sedimentation rate	Sedimentation rate measures how long it takes red blood cells (erythrocytes) to settle in a test tube over a given period. People with FMF have an elevated sedimentation rate, which is an indication of inflammation
Exploratory analyses	Analyses which are performed on the data generated by a study to answer questions which were not the primary focus of the study but which are of interest to the researchers; these analyses may help the researchers to answer new questions which have arisen based on the results of the study or to decide on new questions to investigate in future studies
Febrile	Feverish
Familial Mediterranean fever	Usually, an autosomal recessive syndrome and is caused by mutations of the MEFV gene: occasionally cases of heterozygous FMF (people with only a single copy of a MEFV mutation) are observed suggesting that the disease may be more accurately referred to as variably penetrant autosomal dominant but with gene dosage effect
Hyperimmunoglobulin D syndrome/ mevalonate kinase deficiency	An autosomal recessive syndrome caused by mutations in the mevalonate kinase gene
Glucocorticoids	A class of corticosteroids that has anti-inflammatory and immune system suppressing actions
Periodic fever syndrome	Several different auto-inflammatory diseases that have similar symptoms. The primary symptom being a recurrent fever for which no infectious cause can be found
Serum amyloid A	A type of protein produced by the body in response to infection, tissue injury and malignancy. See amyloidosis
Tumour necrosis factor receptor associated periodic syndrome	An autosomal dominant syndrome caused by a mutation of the TNFRSF1A gene

1. Introduction

Disease background

1.1 Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome /mevalonate kinase deficiency (HIDS/MKD) and familial Mediterranean fever (FMF) are inherited auto-inflammatory conditions classified under a single term of periodic fever syndromes. Periodic fever syndromes may be caused by different genetic defects. The underlying gene defects lead to abnormal activation of the innate immune system, leading to dysregulation of cytokines (such as interleukin-1 beta) and excessive inflammation (European public assessment report [EPAR] for canakinumab). There is overlap in the clinical features across the periodic fever syndromes. These include recurrent episodes of systemic inflammation accompanied by fever and characteristic symptoms and signs in target organs and body systems. People with these conditions may develop amyloidosis (a condition in which an abnormal protein called amyloid builds up in tissues and organs), which can lead to kidney or liver failure.

1.2 TRAPS is an autosomal dominant disorder that affects mostly people of northern European descent. The median age of onset is 3 years (EPAR: canakinumab). The recurrent fever episodes usually lasts around 3 weeks but can last from days to months. The time between episodes can vary from weeks to years. Fevers are often associated with other symptoms such as a rash, puffiness and swelling around the eyes and inflammation in various other areas of the body including the heart muscle, joints, throat, or mucous membranes.

1.3 MKD is a spectrum of disease, ranging from mild to severe complications. HIDS is part of this spectrum (National organisation for rare disorders: mevalonate kinase deficiency). HIDS/MKD is an autosomal recessive disease. Febrile attacks last 3 to 7 days and may occur every 4 to 6 weeks (EPAR: canakinumab). The first attack usually takes place during infancy and can occur spontaneously or be triggered, for example by

emotional or physical stress (Genetic and Rare Diseases Information Centre: hyperimmunoglobulin D syndrome). The attacks are associated with symptoms including cold chills, lymphadenopathy (swollen lymph nodes), abdominal pain, and diarrhoea. There may be no symptoms between attacks, however, in some people, the attacks may be so frequent that the symptoms persist.

1.4 FMF is usually an autosomal recessive disease that affects mainly people of Mediterranean ancestry. Approximately 90% of people with FMF experience the onset of disease before the age of 20 years (EPAR: canakinumab). Fever episodes may last 1 to 3 days (uptodate.com: periodic fever syndromes and other auto-inflammatory diseases). Associated symptoms are similar to TRAPS. In addition, amyloidosis, which can lead to kidney failure, is the most severe complication which can occur if FMF is not treated (Genetic and Rare Diseases Information Centre: familial Mediterranean fever). Variably penetrant autosomal dominant forms of FMF are increasingly recognised (see table of definitions above).

Focus of review

1.5 In line with the marketing authorisation, the focus of this review is on canakinumab for treating the following auto-inflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older:

- tumour necrosis factor receptor associated periodic syndrome (TRAPS),
- hyperimmunoglobulin D syndrome /mevalonate kinase deficiency (HIDS/MKD)
- familial Mediterranean fever (FMF) in combination with colchicine, if appropriate.

Epidemiology and needs assessment

1.6 In England, the estimated prevalence in children and adults that are treated is reported to be 207 with TRAPS, 38 with HIDS/MKD and 40 with cr-FMF. These numbers are based on expert clinical advice.

1.7 TRAPS, HIDS/MKD and FMF are rare conditions with limited treatment options. Current clinical treatment includes the use of NSAIDs (for all conditions) and glucocorticoids (for TRAPS and HIDS/MKD only) to manage fever, inflammation and pain associated with the conditions. However, these treatments do not control the underlying cause of the symptoms or reduce the frequency of attacks. Continued use of glucocorticoids and NSAIDs are associated with adverse effects such as osteoporosis and increased risk of gastrointestinal and cardiovascular events, respectively. Also, in children, glucocorticoids may suppress growth and may affect puberty (British National Formulary for Children). Colchicine is also used in people with FMF to control fever attacks and to prevent secondary amyloidosis. However, colchicine is not licensed for the treatment of FMF in adults. Colchicine is licensed for the treatment of children with FMF for prophylaxis of attacks and prevention of amyloidosis. Colchicine is associated with adverse effects of diarrhoea and transient elevation of transaminases (liver enzymes) and the rare adverse effects of liver dysfunction, leukopenia (low white blood cells), and neuromyopathy (disease affecting nerves and muscles). People with FMF who do not respond to, or are intolerant of colchicine have very few treatment options (EPAR: canakinumab).

1.8 Acute flares of fever often last for a number of days, and symptoms such as extreme tiredness may extend beyond the flare itself therefore people with the condition may be prevented from taking part in daily activities because of uncertainty and concern over subsequent flares. Apart from canakinumab, there are no other biologics that are licensed to treat people with TRAPS, HIDS/MKD and FMF.

1.9 TRAPS, HIDS/MKD and FMF are one of several auto-inflammatory diseases that are being surveyed throughout Europe in the Eurofever

project. This includes a survey on the prevalence of diagnosed or suspected auto-inflammatory diseases among all European paediatric rheumatology centres, an international registry and a survey on the efficacy of treatment in these disorders.

Product overview

Mode of action

1.10 Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1 kappa isotype. It binds specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators (summary of product characteristics: canakinumab).

Regulatory status

1.11 Canakinumab received a market authorisation for the treatment of cryopyrin-associated periodic syndromes (CAPS, a type of periodic fever syndrome) in July 2009. Additional indications have been approved for the treatment of gouty arthritis and for the treatment of Still's disease including adult-onset Still's disease and systemic juvenile idiopathic arthritis. These licensed indications described are outside the scope of this evidence review.

1.12 A licence extension for canakinumab was approved in December 2016 for the treatment of 3 additional periodic fever syndromes, TRAPS, HIDS/MKD and FMF in combination with colchicine, if appropriate in adults, adolescents and children aged 2 years and older.

Dosing information

1.13 Canakinumab is available as a 150 mg/ml solution for subcutaneous injection. The recommended starting dose for the treatment of TRAPS, HIDS/MKD and FMF is 150 mg for people with body weight greater than 40 kg and 2 mg/kg for people with body weight between 7.5 kg and 40 kg. This is administered every 4 weeks as a single dose. A second

dose of 150 mg or 2 mg/kg can be considered if a satisfactory clinical response has not been achieved 7 days after starting the treatment. Once treatment response is subsequently achieved with the additional dose, the intensified dosing regimen of 300 mg (for people weighing greater than 40 kg) or 4 mg/kg (for people weighing 40 kg or less) every 4 weeks is maintained. Those who respond adequately after the first dose are maintained on 150 mg (for people weighing greater than 40 kg) or 2 mg/kg (for people weighing 40 kg or less) every 4 weeks. If there is no clinical improvement with continued treatment, then the need for treatment should be reviewed.

1.14 Canakinumab is associated with an increased incidence of serious infections. People taking canakinumab should be monitored carefully for signs and symptoms of infections during and after treatment. Clinicians should be careful when administering canakinumab to people with infections, a history of recurring infections, or underlying conditions which may predispose them to infections. People with TRAPS, HIDS/MKD or FMF must be evaluated for both active and latent tuberculosis infection before starting treatment with canakinumab and monitored closely for signs and symptoms of tuberculosis during and after treatment. White blood cell counts, including neutrophil counts, should be assessed before starting treatment and again after 1 to 2 months, or periodically for chronic or repeated treatment. Treatment with canakinumab should not be started or continued in people during an active infection requiring medical intervention.

Treatment pathway and current practice

1.15 A diagnosis of TRAPS or HIDS/MKD is made based on clinical evaluation, identification of characteristic symptoms (for example long or life-long lasting fever episodes), and blood tests for inflammatory markers. A diagnosis of TRAPS is usually confirmed by molecular genetic testing, which can identify mutations in the TNFRSF1A gene (National organisation for rare disorders: tumour necrosis factor receptor-associated periodic syndrome). For HIDS/MKD diagnostic tests include assessing the

levels of immunoglobulin D (IgD) in the blood (although currently this is less commonly performed because of poor specificity and sensitivity in this context), urine tests to detect the presence of mevalonate kinase (an assay which is very dependent on methodology and whether the person is febrile or not at the time of sampling, with overall debatable sensitivity and specificity), and DNA analysis to detect the genetic mutation associated with the disorder (bi-allelic mutations in the MVK gene that causes the disorder) (National organisation for rare disorders: mevalonate kinase deficiency).

1.16 FMF is diagnosed based on its characteristic symptoms, a detailed patient history, clinical evaluation and a variety of specialised tests such erythrocyte sedimentation rate during an active episode. Blood tests can also reveal elevated levels white blood cell levels, which are indicative of an immune system response, elevated C-reactive protein (CRP), during periods of inflammation, and elevated levels of fibrinogen (a substance that helps stop bleeding). However, these tests are only abnormal during an episode of FMF, and they return to normal or near normal when an episode ends. Urinary examination may reveal excess loss of a protein called albumin, which can be indicative of kidney disease caused by amyloid A (AA) amyloidosis. A diagnosis of FMF can be confirmed by molecular genetic testing, which can identify the characteristic MEFV gene mutations that cause the disorder (National organisation for rare disorders: familial Mediterranean fever).

1.17 Current treatment for TRAPS, HIDS/MKD and FMF involves early and rapid control of disease activity, prevention of disease and treatment-related damage, enabling participation in daily activities and improvement of health-related quality of life (ter Haar et al. 2015).

1.18 The single hub and access point for paediatric rheumatology in Europe (SHARE) recommends that NSAIDs for all conditions or short-term glucocorticoids (with or without NSAIDs) may be given during inflammatory attacks (ter Haar et al. 2015) for people with TRAPS and MKD/HIDS. The beneficial effect of glucocorticoids has been reported by

SHARE to decline over time so that increasing doses are needed to achieve an equivalent response. SHARE also recommends that IL-1 blockade is beneficial in most people with TRAPS and short-term IL-1 treatment may be effective for stopping inflammatory attacks in people with MKD, therefore should be considered to limit or prevent steroid-related side-effects. SHARE do not recommend colchicine and statins for people with MKD because of lack of efficacy, and the use of anti-tumour necrosis factor (TNF) monoclonal antibodies in TRAPS is also not advised, because of the possible detrimental effect. In selected cases of MKD with severe refractory disease with poor health-related quality of life, SHARE recommends referral to a specialist centre for consideration of allogeneic haematopoietic stem cell transplantation.

1.19 For people with FMF, colchicine is recommended by the European League Against Rheumatism (EULAR) to prevent FMF attacks and associated amyloidosis. EULAR also recommends co-administration of colchicine with alternative biological therapies as it may reduce the risk of amyloidosis despite persistence of attacks (Ozen et al. 2015).

1.20 According to the EPAR for canakinumab, anakinra (a human IL-1 receptor antagonist) and etanercept (a TNF-alpha inhibitor) might be effective treatment options for periodic fever syndromes, however neither is currently licensed for the treatment of TRAPS, HIDS/MKD and FMF. Anakinra may have a practical limitation because of the need for daily injections. NHSE have a clinical commissioning policy for anakinra treatment for people with TRAPS, HIDS/MKD and FMF.

2. Evidence

Literature search

2.1 A literature search was done, which identified 275 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 32 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 5 studies were included in the clinical

evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

2.2 The company submission highlighted studies that were identified in the literature search. In addition, 1 unpublished paper (Lachmann et al. in press) was highlighted, reporting health-related quality of life results from the included pivotal study (De Benedetti.et al. 2018). The data from the unpublished paper is academic-in-confidence (AIC) data and is underlined and highlighted in yellow throughout the evidence review.

2.3 During the scoping phase, 19 papers were also highlighted of which 15 papers had already been identified from the literature search. The remaining 4 papers did not fall within the search parameters.

Overview of included studies

2.4 One randomised controlled trial (RCT) (De Benedetti.et al. 2018) and 4 phase 2 open-label studies were identified from the search (Arostegui et al. 2017, Brik et al. 2014, Gattorno et al. 2017 and Gul et al. 2015). The study by De Benedetti et al. (2018) was the pivotal study that compared canakinumab with placebo in people with TRAPS, MKD and colchicine-resistant FMF (cr-FMF, incomplete response to adequate colchicine doses) in separate groups over a total period of 112 weeks. The study was split into 4 parts (1: screening phase [12 weeks]; 2: randomised treatment phase [16 weeks]; 3: randomised withdrawal and open-label treatment phase [24 weeks]; 4: open-label extension phase [72 weeks]). De Benedetti et al. (2018) reported results from parts 2 and 3 only. Lachmann et al. (in press) (unpublished paper) reported the health-related quality of life results from parts 2 and 3 of the study by De Benedetti et al. (2018).

2.5 The 4 phase 2 open-label studies were single-arm studies that either included people with TRAPS, MKD or cr-FMF and all measured efficacy of canakinumab relative to baseline values. All 5 studies included in the evidence review were also included in the EPAR for canakinumab. A

summary of the characteristics of the included studies is shown in table 1 (see appendix 3, evidence tables for details).

2.6 The information in the unpublished paper by Lachmann et al. (in press) was not summarised into a separate evidence table as the pivotal study from which these results are based has already been summarised in an evidence table (appendix 3, table 4) and therefore not considered as an additional study. These results were summarised with the primary and secondary outcome results of De Benedetti et al. (2018), see appendix 4, table 9.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
De Benedetti et al. 2018 (pivotal study), RCT	People aged 2 years or more with TRAPS (n=46), MKD[a] (n=72) and cr-FMF (n=63)	Intervention: canakinumab 150 mg or 2 mg/kg if weight 40 kg or less by subcutaneously every 4 weeks[b] during part 2 Comparator: placebo	Proportion of participants with complete response, defined as resolution of flare at day 15 and no new flare until week 16
Arostegui et al. 2017, phase 2 open-label study	People with HIDS[a] were on average 16 years (range 5.4 to 29.2 years) n=9	Intervention: canakinumab 300 mg (or 4 mg/kg if weight 40 kg or less) subcutaneously once every 6 weeks during the treatment period[b] No comparator	Reduction in the frequency of attacks during the treatment period compared with historical period
Brik et al. 2014, phase 2 open-label study	Children with cr-FMF median age 9.5 years (range 6.8 to 14.9 years) n=7	Intervention: 3 subcutaneous injections of canakinumab 2 mg/kg (maximum 150 mg) were administered 4 weeks apart[b] No comparator	Proportion of participants with 50% or more reduction in the frequency of FMF attacks during the treatment period compared with the pre-treatment period
Gattorno et al. 2017, phase 2 open-label study	People with TRAPS had a mean age of 34 years (6 participants were less than 18 years of age) n=20	Intervention: canakinumab 150 mg or 2 mg/kg if weight 40 kg or less by subcutaneously every 4 weeks[b] No comparator	Proportion of participants with active TRAPS achieving complete or almost complete response at day 15

Study	Population	Intervention and comparison	Primary outcome
Gul et al. 2015, phase 2 open-label study	People with cr-FMF had a median age of 22 years (range 12 to 34 years) n=9	Intervention: 3 subcutaneous injections of canakinumab 150 mg at 4-week intervals[b] No comparator	Proportion of participants with 50% or more reduction in time-adjusted frequency of attacks

[a] MKD and HIDS are the same condition, the studies including this population used either or both terms to describe them.

[b]See appendix 3 for further dosing information corresponding to the study.

Abbreviations:

cr-FMF, colchicine-resistant familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; MKD, mevalonate kinase deficiency; TRAPS, tumour necrosis factor receptor associated periodic syndrome;

Key outcomes

2.7 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 2 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4. The results are presented by outcomes and the type of periodic fever syndrome (TRAPS, HIDS, MKD and cr-FMF).

Effectiveness

2.8 Primary outcomes in the studies were complete and/or almost complete response and frequency of attacks. The definitions of these varied among the studies. See appendix 3, evidence tables for outcome definitions used in the studies.

Complete response (primary outcome)

2.9 Complete response was defined in De Benedetti et al. (2018) as resolution of the index flare at day 15 and no new flare until week 16 of the study. A similar definition was given in the study by Gattorno et al. (2017). Fever and clinical signs and symptoms were used alongside inflammatory markers that rise during a flare to assess this outcome. This outcome looked at how well canakinumab resolved the flares when they occurred.

2.10 **TRAPS:** De Benedetti et al. (2018) found that there was a statistically significant difference in the number of participants with TRAPS who had a complete response with canakinumab (10/22) compared with placebo (2/24), (45% versus 8%, odds ratio [OR] 9.17 [95% confidence interval [CI] 1.51 to 94.6] p=0.006), at week 16 (part 2). Complete response was maintained up to week 40 in 83% of the participants who had a complete response on either 150 mg or 300 mg at week 16 (n=18). Subgroup analyses by age for this outcome found that 33.3% (3/9) of children aged between 2 to 12 years had a complete response with canakinumab compared with none (0/8) in the placebo group. Forty percent (2/5) of the participants aged between 12 to 18 years achieved a complete response with canakinumab compared with 20% (1/5) in the placebo group. In participants aged 18 years or more, 62.5% (5/8) achieved a complete response with canakinumab compared with 9.1% (1/11) in the placebo group.

2.11 Gattorno et al. (2017) found that 95% (19/20) of the participants with TRAPS had complete or almost complete response of their flare with canakinumab (95% CI 75.1% to 99.9%) at day 15 of the study. This included 4 non-responders at day 8 of which 2 were given an additional dose of canakinumab and the remaining 2 did not receive an additional dose.

2.12 **HIDS/MKD:** De Benedetti et al. (2018) found that there was a statistically significant difference in the number of participants with MKD who had a complete response with canakinumab (13/37) compared with placebo (2/35), (35% versus6%. OR 8.94 [95% CI 1.72 to 86.4] p=0.003) at week 16 (part 2). Complete response was maintained up to week 40 in 82% of the participants with either 150 mg or 300 mg at week 16(n=28). Subgroup analyses by age for this outcome found that 27.8% (5/18) of children aged between 2 to 12 years had a complete response with canakinumab compared with 5.3% (1/19) in the placebo group. Forty percent (4/10) of the participants aged between 12 to 18 years achieved a complete response with canakinumab compared with 14.3% (1/7) in the

placebo group. In participants aged 18 years or more, 44.4% (4/9) achieved a complete response with canakinumab compared with none (0/9) in the placebo group.

2.1 **Cr-FMF:** De Benedetti et al. (2018) found that there was a statistically significant difference in the number of participants with cr-FMF who had a complete response with canakinumab (19/31) compared with placebo (2/32), (61% versus 6%, OR 23.8 [95% CI 4.38 to 227.5] p<0.001) at week 16 (part 2). Complete response was maintained in all participants who had a complete response with either 150 mg or 300 mg at week 16(n=26).Subgroup analyses by age for this outcome found that 77.8% (7/9) of children aged between 2 to 12 years had a complete response with canakinumab compared with none (0/4) in the placebo group. Sixty percent (3/5) of the participants aged between 12 to 18 years achieved a complete response with canakinumab compared with 9.1% (1/11) in the placebo group. In participants aged 18 years or more, 52.9% (9/17) achieved a complete response with canakinumab compared with 5.9% (1/17) in the placebo group.

Frequency of attacks

2.2 **TRAPS:** Benedetti et al. (2018) found that for participants with TRAPS who did not meet the primary outcome of a complete response at week 16 (n=16), the mean number of flares reported from baseline to week 40 (normalised to 1 year) with canakinumab was 1.2 compared with 10.1 flares in the 12 months before baseline.

2.1 **HIDS/MKD:** De Benedetti et al. (2018) found that for participants with MKD who did not meet the primary outcome of a complete response at week 16 (n=21), the mean number of flares reported from baseline to week 40 (normalised to 1 year) with canakinumab was 2 compared with 14.7 flares in the 12 months before baseline. Arostegui et al. (2017) (primary outcome) found that the number of attacks per participant with HIDS decreased from a median of 5 (range 3 to 12 attacks) during the historical period to a median of 0 (range 0 to 2 attacks) during treatment period 1 (6 months duration). The study also reported that the attacks

reoccurred in 22.2% (2/9) of the participants in the treatment period and in 50% (4/8) during the 24-month extension period compared with 100% (9/9) of the participants before treatment. The median duration of attacks was reported to be 3 days (range 2 to 4) during the treatment period, 4 days (range 2 to 10) during the withdrawal period and 3.5 days (range 2 to 8) during the 24-month extension period on treatment with canakinumab.

2.2 **Cr-FMF:** De Benedetti et al. (2018) found that for participants with cr-FMF who did not meet the primary outcome of a complete response at week 16 (n=16), the mean number of flares reported from baseline to week 40 (normalised to 1 year) with canakinumab was 1.2 compared with 32.5 flares in the 12 months before baseline. Brik et al. (2014) and Gul et al. (2015) (primary outcome) found that most, if not all participants with cr-FMF had a 50% or more reduction in the frequency of attacks during the 12-week treatment periods (85.7% [6/7] and 100% [9/9] respectively) compared with pre-treatment phase (no confidence interval data reported in the either study).

Attack severity

2.3 Attack severity score was defined by the physician's and participant's global assessments of disease activity based on a 5-point scale; 0 (absent signs/symptoms), 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe disease activity). This outcome measured the intensity of the attack and looked at how well canakinumab reduced the intensity.

2.4 **TRAPS:** No data

2.5 **HIDS/MKD:** Changes in attack severity were reported in the study by Arostegui et al. (2017) that included participants with HIDS. At baseline, 9 attacks were reported of which 5 were mild and 4 were moderate in severity. During period 1 (treatment period) 2 attacks were reported of which 1 was mild and the other was moderate. During period 3 (24-month extension), 8 attacks were reported of which 1 had no signs or symptoms, 2 had minimal signs and symptoms and 5 were mild.

2.6 **Cr-FMF:** No data

Resolution of baseline flare

2.7 In people with TRAPS, HIDS/MKD and cr-FMF, resolution of attacks means that the person can be free of the signs and symptoms and improve how they feel. De Benedetti et al. (2018) defined resolution of baseline flare as a physician's global assessment score of less than 2, C-reactive protein (CRP) of 10 mg/l or less or reduction of 70% or more from baseline. This outcome looked at how many people with the condition had their flare resolved. Additional results for the time taken for the flare to resolve with canakinumab have also been included in this outcome for information.

2.8 **TRAPS:** De Benedetti et al. (2018) found that 64% (14/22) of participants with TRAPS treated with canakinumab had a resolution of their baseline flare compared with 21% (5/24) in the placebo group at day 15. Gattorno et al. (2017) found that the time to clinical remission was a median of 4 days (95% CI 3 to 8 days) in people treated with canakinumab. In the same study, all 20 participants relapsed during the 5 month withdrawal phase. The median time to relapse following last canakinumab dose was 91.5 days (95% CI 65 to 117 days).

2.1 **HIDS/MKD:** De Benedetti et al. (2018) found that 65% (24/37) of participants with MKD treated with canakinumab had a resolution of their baseline flare compared with 37% (13/35) in the placebo group at day 15. Arostegui et al. (2017) found that it took a median of 3 days (range 1 to 5 days) for an attack to resolve after the first dose of canakinumab. Seven out of the 9 participants relapsed during the 6-month withdrawal phase. The median time to relapse following last canakinumab dose was 110 days (range 62 to 196 days).

2.2 **Cr-FMF:** De Benedetti et al. (2018) found that 81% (25/31) of participants with cr-FMF treated with canakinumab had a resolution of their baseline flare compared with 31% (10/32) in the placebo group at day 15. Brik et al. (2014) found that 5 out of 7 participants with cr-FMF developed an

attack after the last canakinumab injection, within a median of 25 days (range 5 to 34). Gul et al. (2015) found that among the 5 out of 9 participants who relapsed during the 2 month follow-up phase, the time to the next attack after the last dose of canakinumab was a median of 71 days (range 31 to 78 days).

2.3 The studies reporting the time taken to resolve the attack did not report any baseline data with which to compare canakinumab. Therefore, it was difficult to assess the impact of canakinumab on the time taken to resolve an attack after the canakinumab dose and for the next attack to occur following the last dose of canakinumab.

Physician's global assessment (PGA)

2.4 The PGA measures disease severity taking into account fever and clinical signs and symptoms associated with each disease with the use of a 5-point scale with scores of 0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe) (De Benedetti et al. 2018). The studies by Arostegui et al. (2017) and Brik et al. (2014) reported this outcome using the terms poor, fair/somewhat, good, very good and excellent. This outcome was a patient's or a physician's reported outcome and it looked at how well the disease was controlled with canakinumab treatment

2.5 **TRAPS:** In the study by De Benedetti et al. (2018), there was a statistically significant difference in the number of participants with TRAPS who had a PGA score of less than 2 (no disease or minimal disease associated signs and symptoms) with canakinumab compared with placebo, (45.5% versus 4.2% [p=0.0057]) at week 16. Gattorno et al. (2017) found that all participants (n=20) with TRAPS had a PGA score of less than 2 at day 15 compared with all participants reporting a PGA score of more than 2 at baseline.

2.6 **HIDS/MKD:** In the study by De Benedetti et al. (2018), there was a statistically significant difference in the number of participants with MKD who had a PGA score of less than 2 (no disease or minimal disease associated signs and symptoms) with canakinumab compared with

placebo, (46% versus 5.7% [p=0.0011]) at week 16. Arostegui et al. (2017) found that control of HIDS (assessed by physicians and participants) with canakinumab treatment was reported as good in 44.4% (4/9) or excellent in 55.6% (5/9) of the participants at the end of treatment period 1 compared with no disease control or poor disease control in 66.7% (6/9) and 33.3% (3/9) of the participants respectively, during the historical period. At the end of treatment period 3, 8 participants rated the control of HIDS as being excellent.

2.7 **Cr-FMF:** In the study by De Benedetti et al. (2018), there was a statistically significant difference in the number of participants with cr-FMF who had a PGA score of less than 2 (no disease or minimal disease associated signs and symptoms) with canakinumab compared with placebo, (64.5% versus 9.4% [p<0.0001]) at week 16. Brik et al. (2014) found that the PGA was rated as good (3/7) or very good (4/7) for participants with cr-FMF taking canakinumab compared with very poor (3/7), poor (3/7) and fair (1/7) before treatment. Gul et al. (2015) found that the PGA was rated as good (1/9) and very good (8/9) for participants treated with canakinumab compared with poor (8/9) and fair (1/9) before treatment.

Serological (inflammatory) response

2.8 In people with TRAPS, HIDS/MKD and FMF, there is a rise in a number of inflammatory markers such as C-reactive protein (CRP) and serum amyloid A (SAA) in the body. These are biochemical measures of inflammation. High levels are a sign of inflammation and active disease. It is important to people with the conditions to have their SAA levels to be kept at a low level (dependent on the individual and the severity of the conditions) to avoid complications such as AA amyloidosis that can cause kidney failure. The aim is to get the levels within the required therapeutic range; CRP less than 10 mg/l and SAA of less than 10 mg/l. This outcome looked at how well the CRP and SAA levels were controlled with canakinumab treatment.

2.9 **TRAPS:** In De Benedetti et al. (2018), there was a statistically significant difference in the number of participants with TRAPS who had a CRP level of 10 mg/l or less with canakinumab compared with placebo, (36.4% versus 4.2% [p=0.0298]) at week 16. For the SAA level, a statistically significant difference was found for the participants with TRAPS who had a SAA level of 10 mg/l or less with canakinumab compared with placebo (27.3% versus 0% [p=0.047]) at week 16. Gattorno et al. (2017) found that 60% (12/20) of the participants with TRAPS had serological remission defined as a CRP and SAA level of 10 mg/l or less at day 15 of the study.

2.10 **HIDS/MKD:** In De Benedetti et al. (2018), there was a statistically significant difference in the number of participants with MKD who had a CRP level of 10 mg/l or less with canakinumab compared with placebo, (40.5% versus 5.7% [p=0.0020]) at week 16. There was no statistically significant difference found for participants with MKD who had an SAA level of 10 mg/l or less with canakinumab compared with placebo (13.5% versus 2.9% [p=0.1555]) at week 16. Arostegui et al. (2017) found that the median CRP level was 0.8 mg/l (range 0 to 6 mg/l) at day 15 of the treatment period compared with 117.7 mg/l (range 23 to 165 mg/l) during the historical period in participants with HIDS.

2.11 **Cr-FMF:** In De Benedetti et al. (2018), there was a statistically significant difference in the number of participants with cr-FMF who had a CRP level of 10 mg/l or less with canakinumab compared with placebo, (67.7% versus 6.3% [p<0.0001]) at week 16. There was no statistically significant difference found for participants with cr-FMF who had an SAA level of 10 mg/l or less with canakinumab compared with placebo (25.8% versus 0% [p=0.572]) at week 16. Brik et al. (2014) found that in participants with cr-FMF, the median CRP and SAA levels were 1.3 mg/l and 12.2 mg/l respectively at day 86 (end of treatment period) compared with 74 mg/l and more than 500 mg/l respectively at baseline. Gul et al. (2015) found that in participants with cr-FMF, the median CRP and SAA levels were 0.9 mg/l and 9.69 mg/l respectively at day 86 (end of treatment period) compared with 58 mg/l and 162 mg/l respectively at baseline.

Canakinumab dose adjustments

2.12 People with TRAPS, HIDS/MKD and FMF may need to have their dose of canakinumab adjusted. In the study by De Benedetti et al. (2018), an additional dose of 150 mg 4-weekly was given to participants who had a persistent baseline flare between days 8 and 14 or lack of resolution at day 15. Also, participants flaring after day 29 could have their dose increased. In part 3 of the study, responders to canakinumab 150 mg 4-weekly were re-randomised at week 16 to receive either 150 mg 8-weekly or placebo. This outcome looked at how many participants needed to make dose adjustments.

2.13 **TRAPS:** De Benedetti et al. (2018) found that an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 53% of participants with TRAPS. An increase in the dose to 300 mg every 4 weeks was needed in 8% of patients with TRAPS.

2.14 **HIDS/MKD:** De Benedetti et al. (2018) found that an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 23% of the participants with HIDS/MKD. An increase in the dose to 300 mg every 4 weeks was needed in 29% of the participants with HIDS/MKD. In people with HIDS, Arostegui et al. (2017) found that during the treatment period, the dose of canakinumab was adjusted for 2 participants.

2.15 **Cr-FMF:** De Benedetti et al. (2018) found that an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 46% of participants with cr-FMF. An increase in the dose to 300 mg every 4 weeks was needed in 10% of participants with cr-FMF. Use of rescue medicines

Rescue medicines

2.16 During an attack, people with TRAPS, HIDS/MKD and c-FMF may need to take rescue medicines such as glucocorticoids and NSAIDs to manage the attack. This outcome looked at how many participants needed to take rescue medicines while on canakinumab.

2.17 **TRAPS**: no data

2.18 **HIDS/MKD**: In people with HIDS, Arostegui et al. 2017 found that 1 participant out of the total 9 received rescue medicines (NSAIDS and glucocorticoids) during an attack.

2.19 **Cr-FMF**: no data

Quality of life

2.20 Health-related quality of life is a broad measure of a person's health and wellbeing and was assessed by different health questionnaires given to the participants. The SF-12 health survey consists of 12 questions over subscales (physical function, pain, general and mental health, vitality, social function, and physical and emotional health) for participants aged 18 years and older. An increase from baseline of 3, 5, and 8 points in the SF-12 physical and mental component summary scores corresponds to a small, moderate and large treatment effect, respectively. The SF-36 health survey is an extended version of the SF-12 health survey. The child health questionnaire-parent form 50 (CHQ-PF50) for participants aged 5 years to less than 18 years of age. The CHQ-PF50 provides summary scores of physical and psychosocial health for a 14-concept health status and wellbeing concepts. An increase from baseline of 2, 5, and 8 points in the CHQ-PF50 physical and psychological component summary scores corresponds to a small, moderate and large treatment effect, respectively. There were no statistical analyses reported for this outcome. This outcome looked at impact of the disease and treatment with canakinumab on health-related quality of life.

SF-12 and SF-36 health survey

2.21 **TRAPS:** [redacted]

[redacted] Gattorno et al.(2017) found that in adults with TRAPS, the mean SF-36 physical component score increased from 41.8 at baseline to 49.3 at day 15 and remained high 51.4 at day 113. The mean mental component score increased from 39.3 at baseline to 46.6 at day 15 and remained high 49 at day 113 (mean scores were greater than 50 for age and gender matched US population norm).

2.22 **HIDS/MKD:** [redacted]

2.23 **Cr-FMF:** [redacted]

[redacted] Gul et al. (2015) found that in participants with cr-FMF, the median SF-36 physical component score increased from approximately 30 at baseline to approximately 90 at day 86 and the median mental component score increased from approximately 39 at baseline to approximately 90 at day 86. Both physical and mental component scores remained higher than the baseline values at the end of the study.

CHQ-PF50

2.24 **TRAPS**: Lachmann et al. (in press) [redacted]. Gattorno et al. (2017) found that the

mean CHQ-PF50 physical component score increased from 35.4 at baseline to more than 40 at days 15 and 113 in children with TRAPS. However, the mean CHQ-PF50 psychological component score was higher at baseline (52.7) compared with the scores on days 365 and 617 (during the extension phase), when they were reported to be 46.6 and 47.2, respectively.

2.25 [redacted]

2.26 **Cr-FMF:** [redacted]

[redacted] Brik et al. (2014) found that the median CHQ-PF50 physical component score increased from 21 at baseline to 46 at day 86 and the median CHQ-PF50 psychological component score increased from 31 at baseline to 40 at day 86.

Safety and tolerability

2.27 No deaths, opportunistic infections or cancers were reported in any of the included studies.

2.28 **Adverse events:** In De Benedetti et al. (2018), there were more adverse events with canakinumab during the treatment period (part 2) compared with placebo (497 versus 136).However, the participants in the canakinumab group with TRAPS, MKD and cr-FMF had a longer exposure (12.1, 19.1 and 16.4 patient-years, respectively) compared with the combined placebo group (8 patient-years) to canakinumab (when the participants in the placebo group flared they received a dose of canakinumab). The most frequently reported adverse events were infections (particularly respiratory infections), abdominal pain, headaches, and injection-site reactions. The EPAR states that all infections were mild to moderate in severity. In people with TRAPS, Gattorno et al. (2017) found that all participants reported at least 1 adverse event that included nasopharyngitis (60%), abdominal pain (55%), headache (55%), oropharyngeal pain (55%) and fever (50%). Most of the adverse events were reported to be mild to moderate. In people with HIDS, Arostegui et al. (2017) found that all participants experienced at least 1 adverse event. An adverse event of fungal vaginitis was thought to be related to canakinumab. Most frequent adverse events were related to suspected infections (43.9%) that often needed treatment with systemic antibiotics. These were reported to be mild in intensity except for 1 non-serious adverse event of cellulitis being rated as moderate. In people with cr-FMF, Brik et al. (2014) found that 4 of the 9 participants reported 11 adverse events of which 2 were infections and were all reported to be mild except for streptococcal throat infection which was moderate. Gul et al. (2015) found that 8 of the 9 participants reported at least 1 adverse event of

which, headache and upper respiratory tract infection were the only adverse events reported by more than one participant. All were reported to be mild to moderate except for 1 which was a severe headache.

2.29 **Serious adverse events:** In De Benedetti et al. (2018), there were more serious adverse events with canakinumab during the treatment period (part 2) compared with placebo (21 versus 8). Twelve infections were serious that were reported to have resolved. Three serious infections (cellulitis [skin infection], pelvic abscess, and pharyngotonsillitis [sore throat and infection of tonsils]) were reported in 2 participants with cr-FMF receiving canakinumab, and 7 serious infections (3 cases of pneumonia and 1 each of pharyngitis [sore throat], laryngitis [inflammation of voice box], gastroenteritis [gut infection], and conjunctivitis [eye infection]) were reported in 6 participants with MKD taking canakinumab. In people with TRAPS, Gattorno et al. (2017) found that 7 participants reported a serious adverse event that included pericarditis (inflammation of the pericardium which is the sac which surrounds the heart), abdominal pain, diarrhoea, intestinal obstruction, vomiting, and upper respiratory tract infection. In people with HIDS, Arostegui et al. (2017) found that 4 participants reported 14 serious adverse events of which 8 occurred in 1 participant who had systemic amyloid A amyloidosis, a kidney transplant, along with other complications. One participant experienced hidradenitis suppurativa (a type of skin disease) requiring hospitalisation.

2.30 **Discontinuations:** De Benedetti et al. (2018) found 4 participants discontinued treatment with canakinumab. Two participants with MKD discontinued in the treatment period (part 2), 1 because of a disease flare and the other because of pericarditis (possibly indicating lack of efficacy). Two participants with TRAPS discontinued in the open-label period (part 3), 1 because of grade 2 neutropenia (low white blood cells), which was considered by the investigator to be related to canakinumab that resolved in 5 days, and the other had a mild reduction in the glomerular filtration rate (measure of kidney function), which was considered to be unrelated to canakinumab.

2.31 The EPAR states that the safety profile of canakinumab did not differ markedly from the already known and described profile in the already approved indications. The summary of product characteristics for canakinumab states that more than 2,600 people have been treated with canakinumab, including children, healthy volunteers and people in interventional studies with CAPS, TRAPS, HIDS/MKD, FMF, systemic juvenile idiopathic arthritis, gouty arthritis or other interleukin-1 beta mediated diseases. The SPC states that canakinumab is associated with an increased incidence of serious infections and that patients should be monitored carefully for signs and symptoms of infections during and after treatment. Caution should be exercised when treating people with infections, a history of recurring infections or underlying conditions that may predispose them to infections. The EPAR states that there seems to be a slight tendency for increased rates of haematological changes and changes in creatinine levels with higher cumulative doses. The incidence of adverse events were higher in the canakinumab treatment group that received more than 600 mg compared with participants on 600 mg or less.

2.32 The SPC states that the most frequent adverse effects were infections predominantly of the upper respiratory tract. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment. Hypersensitivity reactions and opportunistic infections have been reported in people treated with canakinumab. The SPC further states that there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in children compared with the overall population. The EPAR suggests that females may have more adverse events when treated with canakinumab compared with males.

Evidence gaps and limitations

2.33 The results from the studies suggest canakinumab may be effective for treating flares (or ‘attacks’), reducing the number and intensity of flares, reducing CRP and SAA and improving disease control and health-related quality of life in people with TRAPS, HIDS/MKD and cr-FMF. On

withdrawal of canakinumab in the studies that had a withdrawal or follow-up phase, over half of the participants relapsed.

2.34 The EPAR states that the primary and secondary outcomes of the pivotal study were more robust than the ones used in the phase 2 studies and adequate to demonstrate a clinically relevant treatment response. The main limitations of the studies, particularly the phase 2 open-label studies include their small size, lack of control groups and their open-label nature, which mean they are subject to bias and confounding. Most of the studies were of a short duration and so long-term efficacy and safety data are limited in people with TRAPS, HIDS/MKD and FMF. No data are available for people with renal or hepatic impairment and there are limited data on using canakinumab in pregnant women. The methods used to examine some outcome measures were not clearly reported in the open-label studies. Numerical data and statistical analyses for some of the efficacy outcomes were not clearly reported in the open-label studies. Baseline data were missing for some outcomes in the open-label studies and so a comparison before and after treatment could not be made.

2.35 In De Benedetti et al. (2018), although the numbers recruited for each disease cohort were small, the EPAR states that the numbers that were recruited and randomised are sufficient to evaluate efficacy. There was some uncertainty in using the same outcome measures for TRAPS, HIDS/MKD and cr-FMF because they present with different clinical presentations. For example, frequent serositis is a clinical presentation of FMF and TRAPS but not in HIDS/MKD. The authors of the study reported that they chose a definition of flare that was based on the PGA score and CRP level to account for the differences in the clinical presentations.

2.36 There are limited data for people with FMF who have no prior use of colchicine.The EPAR states that there is biological plausibility that canakinumab would have similar effect in the treatment of FMF without colchicine.

2.37 De Benedetti et al. (2018) compared canakinumab treatment with placebo and there were no other active comparators to assess place in therapy. Also, there was no data reporting outcomes that were considered to be important such as effect on growth, work/school attendance, fertility, long-term complications such as AA amyloidosis and medication burden to manage associated symptoms.

2.38 The EPAR states that subgroup analyses with regard to age, prior use of biological therapy and concomitant use of colchicine did not show any clear signals of reduced or improved efficacy in the pivotal study.

Table 2 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Complete response	De Benedetti et al. 2018	9/10	Directly applicable	B	Complete response was a measure for participants with a complete response to canakinumab treatment during a flare (or 'attack') using clinical measure of severity/disease activity (using the PGA) and biochemical measure of inflammation (using the CRP level). In De Benedetti et al. (2018) with: • 46 people with TRAPS reported a statistically significant difference in the number of participants who had a complete response with canakinumab compared with placebo at week 16: 45% versus 8%, OR 9.17 (95% CI 1.51 to 94.6) p=0.006 • 72 people with MKD reported a statistically significant difference in the number of participants who had a complete response with canakinumab compared with placebo at week 16: 35% versus 6%. OR 8.94 (95% CI 1.72 to 86.4) p=0.003 • 63 people with cr-FMF reported a statistically significant difference in the number of participants who had a complete response with canakinumab compared with placebo at week 16: 61% versus 6%, OR 23.8 (95% CI 4.38 to 227.5) p<0.001 The results suggest that people with TRAPS, MKD and cr-FMF are more likely to achieve a complete response with canakinumab than with placebo and that the difference between the canakinumab treatment and placebo is because of the true treatment effect of canakinumab. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who are
	Gattorno et al. 2017	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
Frequency or recurrence of flares	De Benedetti et al. 2018	9/10	Directly applicable	B	Frequency or recurrence of attacks was a measure to see how many flares occurred during treatment with canakinumab in participants with TRAPS, HIDS/MKD and cr-FMF. In De Benedetti et al. (2018) found that for participants who did not meet the primary outcome of a complete response at week 16 there was a decrease in the mean number of flares up to week 40 (normalised to 1 year) of the study compared with 12 months before baseline in participants with: TRAPS (n=16):,mean number of 1.2 flares compared with a mean number of 10.1 flares respectively HIDS/MKD (n=21): mean number of 2.0 flares compared with a mean number of 14.7 flares respectively Cr-FMF (n=16): mean number of 1.2 flares compared with a mean number of 32.5 flares respectively The results suggest that the frequency or recurrence of attacks is likely to be reduced by canakinumab treatment in people with TRAPS, HIDS and cr-FMF. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, no statistical analyses, inclusion of only people with FMF who are colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
	Arostegui et al. 2017	6/10	Directly applicable		
	Brik et al. 2014	6/10	Directly applicable		
	Gul et al. 2015	6/10	Directly applicable		
Attack severity	Arostegui et al. 2017	6/10	Directly applicable	B	Attack severity was a measure of intensity of an attack and the score was based on the physician's and participants global assessments using a 5-point scale; absent signs/symptoms (score 0) to severe disease activity (score 4). Arostegui et al. 2017 with 9 participants with HIDS, reported 9 attacks at baseline of which 5 were mild and 4 were moderate in severity. During the 6-month treatment period, 2 attacks were reported, 1 was mild and the other was

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					moderate. During the 24-month extension, out of the 8 attacks reported, 1 had no signs or symptoms, 2 had minimal signs and symptoms and 5 were mild. These results suggest that treatment with canakinumab is likely to reduce the severity of attacks in people with HIDS. Results should be interpreted with caution because they are based on a single arm study. It means that it did not randomise patients or compare canakinumab with any other treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that canakinumab is any better or worse than other treatments for this outcome. Also the study was small, and included only people with HIDS. The dose of canakinumab administered was 6-weekly compared with the licensed frequency of 4-weekly.
Resolution of baseline flare	De Benedetti et al. 2018	9/10	Directly applicable	B	Resolution of attack was a measure to see how many participants had their baseline flare resolved with canakinumab. De Benedetti et al. (2018) found that in participants with: TRAPS: 64% (14/22) treated with canakinumab had a resolution of their baseline flare compared with 21% (5/24) in the placebo group at day 15 MKD: 65% (24/37) treated with canakinumab had a resolution of their baseline flare compared with 37% (13/35) in the placebo group at day 15. Cr-FMF: 81% (25/31) treated with canakinumab had a resolution of their baseline flare compared with 31% (10/32) in the placebo group at day 15. Results suggest that in people with TRAPS, MKD and cr-FMF, treatment with canakinumab is likely to resolve the baseline flare compared with no treatment. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, no statistical analyses, inclusion of only people with FMF who are colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Physician's global assessment (PGA)	De Benedetti et al. 2018	9/10	Directly applicable	B	The PGA measure was used to see how well canakinumab controlled the condition taking into account fever and clinical signs and symptoms associated with each disease with the use of a 5-point scale with scores of 0 (none) to 4 (severe). In De Benedetti et al. (2018) with: • 46 people with TRAPS showed a statistically significant difference in the number of participants who had a PGA score of less than 2 with canakinumab compared with placebo at week 16: 45.5% versus 4.2% % OR 23.8 (95% CI 2.52 to 224.9, p=0.0057) • 72 people with MKD showed a statistically significant difference in the number of participants who had a PGA score of less than 2 with canakinumab compared with placebo at week 16: 46% versus 5.7%, OR 13.6 (95% CI 2.83 to 65.6, p=0.0011) • 63 people with cr-FMF showed a statistically significant difference in the number of participants who had a PGA score of less than 2 with canakinumab compared with placebo at week 16: 64.5% versus 9.4% OR 17.0 (95% CI 4.15 to 69.2, p<0.0001) The results suggest that participants with TRAPS, MKD and cr-FMF are more likely to have no disease or minimal disease associated signs and symptoms with canakinumab than with placebo and that the difference between canakinumab treatment and placebo is because of the true treatment effect of canakinumab. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
	Arostegui et al. 2017	6/10	Directly applicable		
	Brik et al. 2014	6/10	Directly applicable		
	Gul et al. 2015	6/10	Directly applicable		
Serological response	De Benedetti et al. 2018	9/10	Directly applicable	B	

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
	Gattorno et al. 2017	6/10	Directly applicable		Serological response is a measure of inflammation that occurs during active disease along with signs and symptoms. High levels (CRP 10 mg/l or more and SAA level 10 mg/l or more) are a sign of inflammation and active disease. In De Benedetti et al. (2018) with: • 46 people with TRAPS reported a statistically significant difference in the number of participants who had a CRP level of 10 mg/l or less with canakinumab compared with placebo at week 16: 36.4% versus 4.2% OR 6.64 (95% CI 1.20 to 36.6, p=0.0298). For the SAA level, a statistical significant difference was reported for the participants who had a SAA level of 10 mg/l or less with canakinumab compared with placebo at week 16: 27.3% versus 0%, OR 16.7 (95% CI 1.04 to 268.5, p=0.047) • 72 people with MKD reported a statistically significant difference in the number of participants who had a CRP level of 10 mg/l or less with canakinumab compared with placebo at week 16: 40.5% versus 5.7%, OR 12.7 (95% CI 2.53 to 63.9, p=0.0020). There was no statistical significant difference reported for participants with an SAA level of 10 mg/l or less with canakinumab compared with placebo at week 16: 13.5% versus 2.9%, OR 5.26 (95% CI 0.53 to 52.0, p=0.1555) • 63 people with cr-FMF reported a statistically significant difference in the number of participants who had a CRP level of 10 mg/l or less with canakinumab compared with placebo at week 16: 67.7% versus 6.3%, OR 29.8 (95% CI 5.86 to 151.3, p<0.0001). There was no statistical significant difference reported for participants with an SAA level of 10 mg/l or less with canakinumab compared with placebo at week 16: 25.8% versus 0%, OR 17.5 (95% CI 0.92 to 332.9, p=0.572) The results suggest that participants with TRAPS, MKD and cr-FMF are more likely to have lower CRP levels with canakinumab than with placebo and that the difference between the canakinumab treatment and placebo is because of the true treatment effect of canakinumab. The results also suggest that people with TRAPS are more likely to have lower SAA levels with canakinumab than with placebo. Although treatment with canakinumab reduced SAA levels in more
	Arostegui et al. 2017	6/10	Directly applicable		
	Brik et al. 2014	6/10	Directly applicable		
	Gul et al. 2015	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					people with MKD and cr-FMF than with placebo, the statistical test suggests that the difference between the 2 treatments is because of random chance rather than the true effect of the treatment. Low levels of SAA can avoid complications such as AA amyloidosis that can cause kidney failure. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
Canakinumab dose adjustments	De Benedetti et al. 2018	9/10	Directly applicable	B	The need for canakinumab dose adjustments was a measure to see if an additional canakinumab dose was needed to resolve a flare In De Benedetti et al. (2018) found that: • For participants with TRAPS, an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 53%. An increase in the dose to 300 mg every 4 weeks was needed in 8% of the participants. • For participants with MKD, an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 23%. An increase in the dose to 300 mg every 4 weeks was needed in 29% of the participants. • For participants with cr-FMF, an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 46%. An

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					increase in the dose to 300 mg every 4 weeks was needed in 10% of the participants. The results suggest that people with TRAPS, MKD and cr-FMF who take a higher dose of canakinumab are more likely to have their fares stopped if the low dose does not provide adequate control. Also, canakinumab administered at 8-weekly intervals may be effective than placebo among responders to 4-weekly canakinumab. However this difference between treatment and placebo is because of random chance rather than true treatment effect of canakinumab. These canakinumab dose adjustment results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
Use of rescue medicines	Arostegui et al. 2017	6/10	Directly applicable	B	The use of rescue medicines was a measure to see how many participants on canakinumab needed rescue medicines to manage flares. Arostegui et al. (2017) with 9 participants with HIDS, reported that during 6 month treatment period, 1 participant received rescue medicines (NSAIDS and glucocorticoids) during an attack. The results suggest fewer people with HIDS may need to take rescue medicines while on canakinumab to treat their flare. Results should be interpreted with caution because they are based on a single arm study. It means that it did not randomise patients or compare canakinumab with any other treatment. Therefore it does not reduce the risk of other factors influencing the results and it does not provide evidence that canakinumab is any better or worse than other treatments for this outcome. Also the study was small, and included only people with HIDS. The dose of canakinumab administered was 6-weekly compared with the licensed frequency of 4-weekly.

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Quality of life measured using SF-12	De Benedetti et al. 2018	9/10	Directly applicable	B	The SF-12 health survey is used to rate a person's (aged 18 years or over) health and wellbeing based on 12 questions about physical function, pain, general and mental health, vitality, social function, and physical and emotional health. Higher scores are better. An increase from baseline of 3, 5, and 8 points in the physical and mental component summary scores corresponds to a small, moderate and large treatment effect, respectively. This outcome looked at how the score changed from baseline with canakinumab treatment. In Lachmann et al. (in press) found that: • [redacted] • [redacted] • [redacted] [redacted]

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					[redacted] These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable, however these results were based on an exploratory analysis (data generated by a study to answer questions which were not the primary focus of the study) with a small number of participants completing the health questionnaire. There are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
Quality of life measured using CHQ-PF50	De Benedetti et al. 2018	9/10	Directly applicable	B	The CHQ-PF50 is a general health-related quality of life questionnaire used in children ages 5 years to less than 18 years of age. It looks at the child's physical, emotional, and social wellbeing from the perspective of a parent or guardian. Higher scores are better. An increase from baseline of 2, 5, and 8 points in the physical and mental/psychological component summary scores corresponds to a small, moderate and large treatment effect, respectively. This outcome looked at how the score changed from baseline with canakinumab treatment. In Lachmann et al. (in press) found that: • [redacted] • [redacted]
	Gattorno et al. 2017	6/10	Directly applicable		
	Brik et al. 2014	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					• [redacted]  These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable, however these results were based on an exploratory analysis with a small number of participants completing the health questionnaire. There are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
Adverse events	De Benedetti et al. 2018	9/10	Directly applicable	B	Adverse events are undesirable events that were not present before the treatment started, or events that were already present but which worsened in intensity or frequency after the treatment. The adverse event may or may not be associated
	Gattorno et al. 2017	6/10	Directly applicable		
	Arostegui et al. 2017	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
	Brik et al. 2014	6/10	Directly applicable		with the treatment. This outcome looks at how many adverse events occurred during the study. In De Benedetti et al. (2018), more participants receiving canakinumab than those receiving placebo had an adverse event (497 versus 136), however the canakinumab treatment group had longer exposure to treatment compared with the placebo group (over 12 patient-years compared with 8 patient-years, respectively) The most frequently reported adverse events were infections (particularly respiratory infections), abdominal pain, headaches, and injection-site reactions. The results suggest that people who have treatment with canakinumab are more likely to experience an adverse event. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
	Gul et al. 2015	6/10	Directly applicable		
Serious adverse events	De Benedetti et al. 2018	9/10	Directly applicable	B	Serious adverse events are undesirable events that were not present before the treatment started, or events that were already present but which worsened in intensity or frequency after the treatment and may result in hospitalisation or stopping treatment. The serious adverse event may or may not be associated with the treatment. This outcome looks at how many serious adverse events occurred during the study. In De Benedetti et al. (2018), more participants receiving canakinumab than those receiving placebo had a serious adverse event (21 versus 8), however the canakinumab treatment group had longer exposure to treatment compared with the placebo group (over 12 patient-years compared with 8 patient-years, respectively) Twelve infections were serious that were reported to have resolved. The results suggest that people who have treatment with canakinumab are at increased risk of experiencing serious infections. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were
	Gattorno et al. 2017	6/10	Directly applicable		
	Arostegui et al. 2017	6/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
					colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.
Discontinuations	De Benedetti et al. 2018	9/10	Directly applicable	B	This outcome considered how many people had to stop taking canakinumab during the study. De Benedetti et al. (2018) found 4 participants discontinued treatment with canakinumab. Two participants with MKD discontinued in during the 16-week treatment period, 1 because of a disease flare and the other because of pericarditis (inflammation of the pericardium which is the sac which surrounds the heart). These were thought to be because of lack of efficacy of canakinumab. Two participants with TRAPS discontinued in during the open-label phase (part 3), 1 because of grade 2 neutropenia (low white blood cells), which was considered by the investigator to be related to canakinumab that resolved in 5 days, and the other had a mild reduction in the glomerular filtration rate (measure of kidney function), which was considered to be unrelated to canakinumab. Results suggest that people taking canakinumab may needs to stop treatment because of adverse events associated with treatment. These results come from a phase 3 double-blind placebo-controlled RCT and are therefore reliable. However, there are some limitations that include the small numbers of people with the condition, inclusion of only people with FMF who were colchicine-resistant and canakinumab treatment was compared with placebo only and no other biologics that may be used in practice.

3. Related NICE guidance and NHS England clinical policies

NICE have not issued any guidelines or policies on managing TRAPS, HIDS/MKD or FMF with canakinumab.

NHSE have the following relevant policy for people with TRAPS, HIDS/MKD and FMF:

- Clinical Commissioning Policy (2018): Anakinra to treat periodic fevers and auto-inflammatory diseases (all ages)

4. References

Arostegui JI, Anton J, Calvo I et al (2017) Open-Label, Phase II Study to Assess the Efficacy and Safety of Canakinumab Treatment in Active Hyperimmunoglobulinemia D with Periodic Fever Syndrome. Arthritis & Rheumatology 69(8): 1679–1688

Bashardoust B (2015) Familial Mediterranean fever; diagnosis, treatment, and complications. Journal of Nephropharmacology 4(1): 5–8

Brik R, Butbul-Aviel Y, Lubin S et al (2014) Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study. Arthritis & Rheumatology 66 (11): 3241–3

De Benedetti, Gattorno M, Anton J et al (2018) Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. The New England Journal of Medicine 378(20): 1908–1919

Gattorno M, Obici L, Cattalini M et al (2017) Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. Annals of the Rheumatic Diseases 76(1): 173–178

Gul A, Ozdogan H, Erer B et al (2015) Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. Arthritis Research & Therapy 17: 243

[redacted]

Ozen S, Demirkaya E, Erer B, et al (2015) EULAR recommendations for the management of familial Mediterranean fever. Annals of the rheumatic diseases 75: 644–651

Ter Haar N, Oswald M, Jeyaratnam J et al (2015) Recommendations for the management of autoinflammatory diseases. Annals of the Rheumatic Diseases 74(9): 1636–1644

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

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Appendix 1 Search strategy

Databases

Database:
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to Present with Daily Update>, Ovid MEDLINE(R) Epub Ahead of Print <July 10, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 10, 2018>
Search date: 11/07/18
Number of results retrieved: 75
Search strategy:

1 canakinumab.ti,ab. (379)
2 ilaris.ti,ab. (16)
3 ACZ885.ti,ab. (6)
4 or/1-3 (382)
5 ("periodic fever syndrome*" or "recurrent polyserosit*").ti,ab. (451)
6 ((periodic or hereditary or familial) adj2 (fever* or autoinflammat*)).ti,ab. (3802)
7 ((("TNF* receptor" or "TNF* associated" or "tumour necrosis factor" or "tumor necrosis factor") and ("associated periodic syndrome" or "associated periodic fever")) or "familial Hibernian fever").ti,ab. (370)
8 TRAPS.ti,ab. (15401)
9 ((dutch adj1 periodic fever) or (("hyper IgD" or hyper-IgD or hyper-immunoglobulin or hyperimmunoglobulin*) and ("periodic fever" or syndrome))).ti,ab. (778)
10 HIDS.ti,ab. (206)
11 (((mevalonic or mevalonate) and (aciduria or "kinase deficienc*")) or mevalonicaciduria*).ti,ab. (264)
12 MKD.ti,ab. (146)
13 ("familial mediterranean fever" or "paroxysmal peritoniti*" or "paroxysmal polyserositides" or (wolff* adj1 "periodic disease") or "periodic peritoniti*" or "periodic polyserositis").ti,ab. (2995)
14 FMF.ti,ab. (2121)
15 hereditary autoinflammatory diseases/ or familial mediterranean fever/ or mevalonate kinase deficiency/ (3847)
16 or/5-15 (21287)
17 4 and 16 (79)
18 limit 17 to english language (75)
19 animal/ not human/ (4439467)
20 18 not 19 (75)

Database: Embase
Platform: Ovid
Version: Embase 1974 to 2018 July 10
Search date: 11/07/18
Number of results retrieved: 254
Search strategy:
1 canakinumab.ti,ab. (969)
2 ilaris.ti,ab. (42)
3 ACZ885.ti,ab. (27)
4 canakinumab/ (2151)
5 or/1-4 (2171)

6 ("periodic fever syndrome*" or "recurrent polyserosit*").ti,ab. (791)
7 ((periodic or hereditary or familial) adj2 (fever* or autoinflammat*)).ti,ab. (5755)
8 ((("TNF* receptor" or "TNF* associated" or "tumour necrosis factor" or "tumor necrosis factor") and ("associated periodic syndrome" or "associated periodic fever")) or "familial Hibernian fever").ti,ab. (593)
9 TRAPS.ti,ab. (16120)
10 ((dutch adj1 periodic fever) or (("hyper IgD" or hyper-IgD or hyper-immunoglobulin or hyperimmunoglobulin*) and ("periodic fever" or syndrome))).ti,ab. (1076)
11 HIDS.ti,ab. (391)
12 (((mevalonic or mevalonate) and (aciduria or "kinase deficienc*")) or mevalonicaciduria*).ti,ab. (389)
13 MKD.ti,ab. (283)
14 ("familial mediterranean fever" or "paroxysmal peritoniti*" or "paroxysmal polyserositides" or (wolff* adj1 "periodic disease") or "periodic peritoniti*" or "periodic polyserositis").ti,ab. (4352)
15 FMF.ti,ab. (3489)
16 familial Mediterranean fever/ or "hyperimmunoglobulinemia D and periodic fever syndrome"/ or tumor necrosis factor receptor associated periodic syndrome/ or recurrent fever/ (7517)
17 or/6-16 (25616)
18 5 and 17 (490)
19 limit 18 to english language (479)
20 limit 19 to (conference abstract or conference paper or "conference review" or letter or note) (225)
21 19 not 20 (254)
22 nonhuman/ not (human/ and nonhuman/) (4190371)
23 21 not 22 (254)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – Issue 6 of 12, June 2018
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 6 of 12, June 2018
HTA – Issue 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 11/07/18
Number of results retrieved: CDSR 0 ; DARE 0 ; CENTRAL 20 ; HTA 0 ; NHS EED 0.
Search strategy:
#1 canakinumab:ti,ab 150
#2 ilaris:ti,ab 3
#3 ACZ885:ti,ab 24
#4 {or #1-#3} 161
#5 ("periodic fever syndrome*" or "recurrent polyserosit*"):ti,ab 12
#6 ((periodic or hereditary or familial) near/2 (fever* or autoinflammat*)):ti,ab 102
#7 ((("TNF* receptor" or "TNF* associated" or "tumour necrosis factor" or "tumor necrosis factor") and ("associated periodic syndrome" or "associated periodic fever")) or "familial Hibernian fever"):ti,ab 15
#8 TRAPS:ti,ab 175
#9 ((dutch adj1 periodic fever) or (("hyper IgD" or hyper-IgD or hyper-immunoglobulin or hyperimmunoglobulin*) and ("periodic fever" or syndrome))):ti,ab 18
#10 HIDS:ti,ab 18

#11 (((mevalonic or mevalonate) and (aciduria or "kinase deficienc*")) or mevalonicaciduria*):ti,ab 14
#12 MKD:ti,ab 21
#13 ("familial mediterranean fever" or "paroxysmal peritoniti*" or "paroxysmal polyserositides" or (wolff* adj1 "periodic disease") or "periodic peritoniti*" or "periodic polyserositis"):ti,ab 80
#14 FMF:ti,ab 79
#15 [mh "hereditary autoinflammatory diseases"] or [mh "familial mediterranean fever"] or [mh "mevalonate kinase deficiency"] 170
#16 {or #5-#15} 424
#17 #4 and #16 20

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 275 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	**Inclusion**	**Exclusion**
Population	Adults, adolescents and children aged 2 years and older with the following autoinflammatory periodic fever syndromes: • TRAPS • HIDS/MKD • FMF	Non-humans People with other types of periodic fever syndromes such as cryopyrin-associated periodic syndromes (CAPS)
Intervention	Canakinumab	
Comparator	• Standard care without canakinumab • Non-steroidal anti-inflammatory drugs (NSAIDS) • corticosteroids • anakinra • etanercept • tocilizumab • allogeneic haematopoietic stem cell transplantation • colchicine	
Outcomes	**Efficacy** • Percentage of patients achieving resolution of baseline symptom flare or absence of new flare • Percentage of patients with serologic remission (C-reactive	None

Sifting criteria	Inclusion	Exclusion
	protein (CRP) levels 10 mg/l or less) • Percentage of patients with normalised serum amyloid A (SAA) levels 10 mg/l or less) • Reduction/control of symptoms associated with the condition • Symptom-free time • Prevention of long-term complications associated with the condition such as amyloidosis, kidney failure, steroid-induced damage • Growth and development in children • Autoinflammatory disease damage index (ADDI) • Reduction in polypharmacy associated with managing individual symptoms • Physician Global Assessment (PGA) score of less than 2 • Number of days with fever **Adverse events** • Overall number of adverse events • Number of severe adverse events • Discontinuations because of adverse events **Other** Survival; progression free survival; health-related quality of life (including mobility; self-care; usual activities; anxiety/depression); replacement of more toxic treatment; dependency on care giver/supporting independence; safety (including adverse effects); and delivery of intervention.	
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies Case series Pharmacokinetic studies

Figure 1 Flow chart of included studies

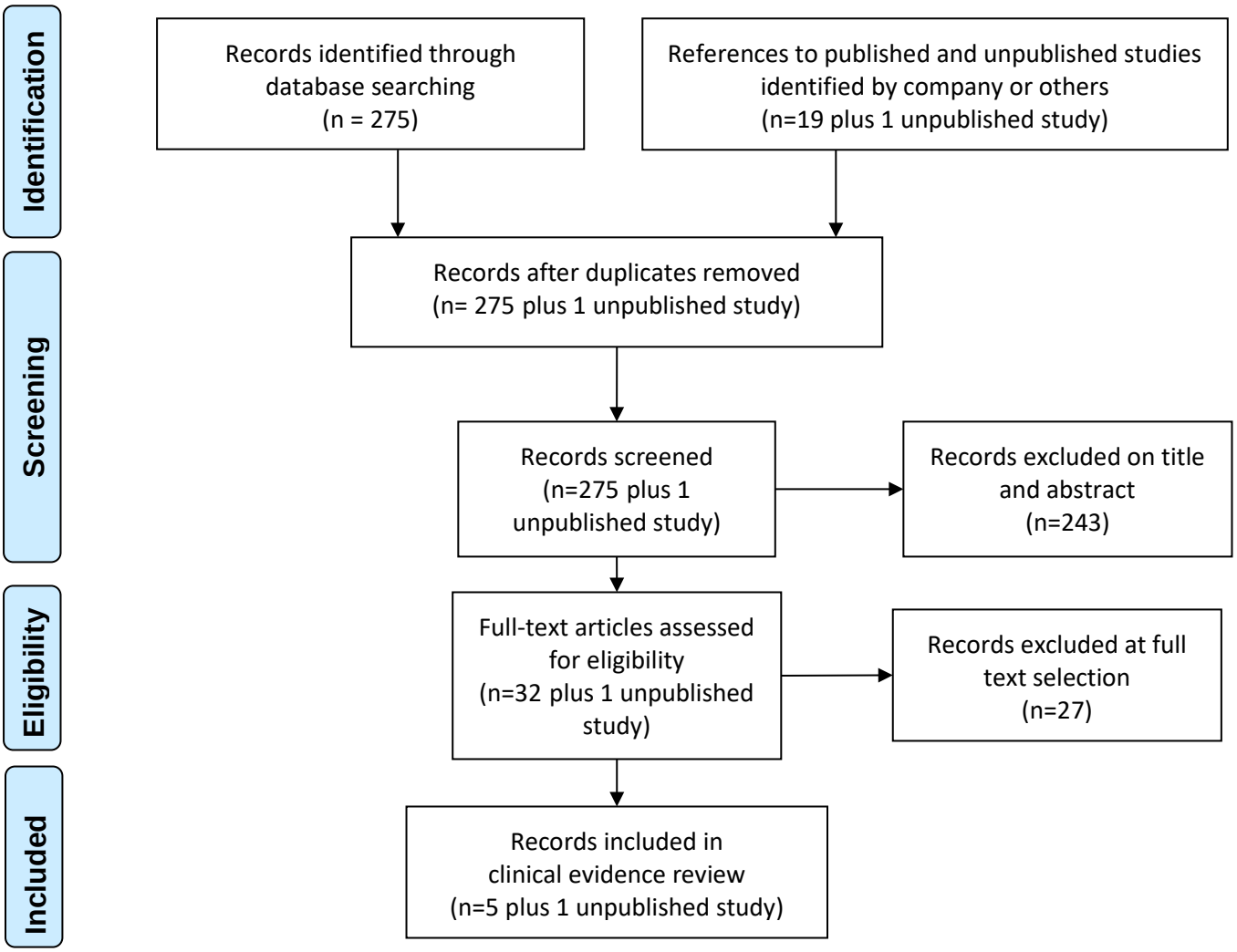

Table 3 Excluded Studies following full text review

Study reference	Reason for exclusion
Akar Servet, Cetin Pinar, Kalyoncu Umut, et al. (2018) Nationwide Experience With Off-Label Use of Interleukin-1 Targeting Treatment in Familial Mediterranean Fever Patients. Arthritis care & research 70(7), 1090-1094	Results for canakinumab treated participants included in this retrospective medical record review not reported separately
Akgul Ozgur, Kilic Erkan, Kilic Gamze, and Ozgocmen Salih (2013) Efficacy and safety of biologic treatments in Familial Mediterranean Fever. The American journal of the medical sciences 346(2), 137-41	Review paper including less than 5 people with FMF
Arostegui J I, Anton J, Calvo I et al. (2016) Long-term efficacy and safety of Canakinumab in active hyper-IgD syndrome (HIDS): Results from an open-label study. Pediatric Rheumatology	Oral presentation
Barranco Caroline (2016) Therapy: Patients with TRAPS respond to canakinumab. Nature reviews. Rheumatology 12(8), 436	Abstract only
Basaran O, Uncu N, Celikel B A et al. (2015) Interleukin-1 targeting treatment in familial mediterranean fever: An experience of pediatric patients. Modern Rheumatology 25(4), 621-624	Case series
Benedetti F, Anton J, Ben-Chetrit E et al. (2017) Efficacy and safety of canakinumab in patients with periodic fever syndromes (colchicine-resistant FMF, HIDS/MKD and TRAPS): results from a phase 3, pivotal, umbrella trial. Arthritis and rheumatology. Conference: 2017 ACR/ARHP pediatric rheumatology symposium. United states 69, 23-24	Abstract only
Brizi Maria Giuseppina, Galeazzi Mauro, Lucherini Orso Maria et al. (2012) Successful treatment of tumor necrosis factor receptor associated periodic syndrome with canakinumab. Annals of internal medicine 156(12), 907-8	Abstract only
Cetin P, Sari I, Sozeri B, Cam O et al. (2014) Efficacy of Interleukin-1 Targeting Treatments in Patients with Familial Mediterranean Fever. Inflammation 38(1), 27-31	Better evidence available[1]
Curtis Casey D, and Fox Charity C (2015) Treatment of adult hyper-IgD syndrome with canakinumab. The journal of allergy and clinical immunology. In practice 3(5), 817-8	Letter of case report

Study reference	Reason for exclusion
Deshayes S, Georgin-Lavialle S, Hot A, Durel C A et al. (2018) Efficacy of continuous interleukin 1 blockade in mevalonate kinase deficiency: A multicenter retrospective study in 13 adult patients and literature review. Journal of Rheumatology 45(3), 425-429	Better evidence available[1]
Frenkel J, Anton J, Hashkes P, Cattalini M et al. (2017) Efficacy and safety of Canakinumab in patients with HIDS/MKD: results from the pivotal phase 3 cluster trial. Pediatric rheumatology. Conference: 24th paediatric rheumatology European society congress. Greece 15, 16	Abstract only
Galeotti Caroline, Meinzer Ulrich, Quartier Pierre, Rossi-Semerano Linda et al. (2012) Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. Rheumatology (Oxford, and England) 51(10), 1855-9	Better evidence available[1]
Gul A, Ozdogan H, Kasapcopur O, Erer B, Ugurlu S, Sevgi S, and Turgay S (2016) Quality of life changes with canakinumab therapy in adults with colchicine-resistant FMF. Pediatric Rheumatology	Poster presentation
Haviv Ruby, and Hashkes Philip J (2016) Canakinumab investigated for treating familial Mediterranean fever. Expert opinion on biological therapy 16(11), 1425-1434	Review paper
La Torre , F , Caparello M, and Cimaz R (2017) Canakinumab for the treatment of TNF receptor associated periodic syndrome. Expert Review of Clinical Immunology 13(6), 513-523	Review paper
Lachmann H, Cattalini M, Obici L et al. (2015) Canakinumab treatment in patients with active recurrent or chronic TNF receptor associated syndrome (TRAPS): Efficacy and safety results from a proof of concept study. Pediatric Rheumatology 13(1), O59	Oral presentation
Laskari K, Boura P, Dalekos G N et al. (2015) The IL-1 inhibitor Canakinumab for Familial Mediterranean Fever: The Greek experience in 12 patients. Pediatric Rheumatology 13(1), P72	Poster presentation
Laskari Katerina, Boura Panagiota, Dalekos George N et al. (2017) Long-term Beneficial Effect of Canakinumab in Colchicine-resistant Familial Mediterranean Fever. The Journal of rheumatology 44(1), 102-109	Better evidence available[1]

Study reference	Reason for exclusion
Nct (2014) Study of Efficacy and Safety of Canakinumab in Patients With Hereditary Periodic Fevers. Https://clinicaltrials.gov/show/nct02059291	Clinical trial link, already included published paper
Ozcakar Z Birsin, Ozdel Semanur, Yilmaz Songul, Kurt-Sukur E Didem, Ekim Mesiha, and Yalcinkaya Fatos (2016) Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. Clinical rheumatology 35(2), 441-6	Case series
Trabulus Sinan, Korkmaz Merve, Kaya Eda, and Seyahi Nurhan (2018) Canakinumab treatment in kidney transplant recipients with AA amyloidosis due to familial Mediterranean fever. Clinical transplantation , e13345	Case series
Ugurlu S, Seyahi E, Hatemi G, Hacioglu A et al. (2016) Canakinumab therapy in patients with Familial Mediterranean Fever. Pediatric Rheumatology ,	Oral presentation
Ummarino Dario (2017) Autoinflammation: Canakinumab effective in HIDS treatment. Nature reviews. Rheumatology 13(7), 388	Abstract only
van der Hilst , Jeroen Ch, Moutschen Michel et al. (2016) Efficacy of anti-IL-1 treatment in familial Mediterranean fever: a systematic review of the literature. Biologics : targets & therapy 10, 75-80	Individual studies already included. Also includes interventions other than canakinumab in the review.
Varan Ozkan, Kucuk Hamit, Babaoglu Hakan, Guven Serdar Can et al. (2018) Efficacy and safety of interleukin-1 inhibitors in familial Mediterranean fever patients complicated with amyloidosis. Modern rheumatology , 1-4	Study reported combined results of anakinra and canakinumab, unable to extract data for canakinumab only.
Wilhelmi E (2017) Canakinumab for the treatment of periodic fever syndrome. Journal fur Pharmakologie und Therapie 26(2), 64-65	Non-English language
Yazilitas Fatma, Aydog Ozlem, Ozlu Sare Gulfem et al. (2018) Canakinumab treatment in children with familial Mediterranean fever: report from a single center. Rheumatology international 38(5), 879-885	Case series
[1] This paper was not prioritised as it was low quality evidence and an RCT and 4 phase 2 studies had already been identified.	

Appendix 3 Evidence tables

Table 4 De Benedetti et al. (2018)

Study reference	De Benedetti F, Gattorno M, Anton J et al. (2018) Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. New England Journal of Medicine 378(20):1908–1919
Unique identifier	NCT02059291
Study type (and NSF-LTC study code)	Phase 3 randomised, double-blind, placebo-controlled study, followed by an open-label phase P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of canakinumab in people with TRAPS, MKD[a] and colchicine-resistant (cr) FMF.
Study dates	June 2014 to July 2017
Setting	Investigators were listed to be in Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Russia, Spain, Switzerland, Turkey, UK and the US
Number of participants	n=46 with TRAPS, n=72 with MKD and n=63 with colchicine-resistant FMF all randomised.
Population	TRAPS Participants with TRAPS were on average aged 22 years and 50% were female. The participants with TRAPS on average had the condition for 13 years with approximately 10 fever episodes reported annually before the trial. MKD Participants with MKD were on average 13 years and approximately 60% were female. The participants with MKD on average had the condition for 12 years with approximately 15 fever episodes reported annually before the trial. Cr-FMF Participants with cr-FMF (incomplete response to adequate colchicine dosing) were on average 22 years and approximately 46% were female. The participants with cr-FMF on average had the condition for 16 years with approximately 24 fever episodes reported annually before the trial. Around 87% of the participants with cr-FMF were on colchicine treatment. On average, 34.8%, 18% and 24% of the participants with TRAPS, MKD and cr-FMF respectively, received 1 or more biologic agents before enrolment. Over half (56%) of the total number of participants enrolled had a PGA score of 3 which is classed as moderate disease and a further 19% had a PGA score of 4 which is classed as severe disease.

Inclusion criteria	TRAPS Participants with TRAPS were included if they has a mutation of the TNFRSF1A gene and chronic or recurrent disease. Recurrent disease was defined as more than 6 episodes per year. MKD Participants with a confirmed genetic or enzymatic diagnosis of MKD were included with historical data documenting at least 3 fever episodes in a 6-month period. cr-FMF Participants with cr-FMF were included if the diagnosis was confirmed by Tel-Hashomer diagnostic criteria, had at least 1 known MEFW exon 10 mutation and historical data documenting at least 1 fever episode per month despite standard dose of colchicine (1.5 to 3 mg/day or equivalent paediatric-adjusted regimen) or at least 1 fever episode per month with unacceptable adverse effects to colchicine. At randomisation, participants must have had an active flare (termed 'index flare' in the study at baseline) characterised by their symptoms specific to the condition and with a PGA score of 2 or more and CRP of more than 10 mg/l.
Exclusion criteria	For the purpose of this evidence table the main exclusion criteria have been listed below see the study protocol for further details. • Use of biologics or corticosteroids within a specified time period before baseline • History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants • History of malignancy of any organ system (other than localised basal cell carcinoma of the skin or in-situ cervical cancer) • Significant medical disease that include organ transplant, elevated ALT, AST or bilirubin, serious hepatic disease, chronic kidney disease, thyroid disease, active peptic ulcer disease, coagulopathy • History or evidence of tuberculosis • Any conditions or significant medical problems which in the opinion of the investigator compromises the participant's immune system such as HIV infection, hepatitis B or hepatitis C infections • Pregnant or nursing women • Live vaccinations within 3 months before the start of the trial, during the trial, and up to 3 months following the last dose

Intervention	Part 2[b] Canakinumab 150 mg or 2 mg/kg in participants weighing 40 kg or less by subcutaneous injection every 4 weeks. All participants were eligible for a blinded dose increase of 1 add-on injection of canakinumab 150 mg if they had a persistent baseline flare[c] between day 8 and 14 or lack of resolution[d] at day 15. After day 29, participants were eligible for an open-label increase in the dose of canakinumab to 300 mg every 4 weeks if they had a flare[e]. Participants in the placebo group could receive 150 mg every 4 weeks after day 29. If they had a flare[e] they could receive 300 mg, or 4 mg/kg for participants weighing 40 kg or less at their next visit. Part 3[b] Participants in the canakinumab group who met the primary outcome in part 2 underwent a second randomisation to receive 150 mg of canakinumab or placebo every 8 weeks. Participants in the placebo group who had a flare[e] within 8 weeks switched to open-label canakinumab 150 mg every 4 weeks and those that had a flare[e] after more than 8 weeks switched to canakinumab 150 mg every 8 weeks. Participants receiving canakinumab every 8 weeks who had another flare[e] were switched back to every 4 weeks at any time. A maximum dose of 300 mg every 4 weeks was given to participants who had a flare[e].
Comparator	Placebo every 4 weeks Rescue medicines that included corticosteroids maintenance dose or intermittent steroid treatment and standard doses of NSAIDs were allowed on an as needed basis to treat the sign and symptoms. of TRAPS, HIDS or cr-FMF during acute flares at the discretion of the investigator. NSAIDs were not allowed for treating any signs or symptoms of the index flare.
Length of follow-up	The trial consisted of a screening period of up to 12 weeks (part 1), a randomised, double-blind, placebo-controlled period of 16 weeks (part 2), a randomised withdrawal and open-label period of 24 weeks (part 3), and an open-label extension period of 72 weeks (part 4).
Outcomes	Primary outcome: • Proportion of participants with complete response, defined as resolution[d] of flare (index flare) at day 15 and no new flare[e] until week 16.

	Secondary outcomes: • Proportion of participants at week 16 (part 2) with a: - PGA score of less than 2 - CRP level of 10 mg/l or less - serum amyloid A (SAA) level of 10 mg/l or less • For part 3, the proportion of participants receiving canakinumab or placebo every 8 weeks who had no new flare[e]. Exploratory objectives reported in the study by Lachmann et al. (in press) included: • [redacted] • [redacted]
	Safety outcomes: • Adverse events • Serious adverse events • Discontinuations
Abbreviations	ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; cr-FMF, colchicine-resistant familial Mediterranean fever; MKD, mevalonate kinase deficiency; PGA, physician's global assessment; SAA, serum amyloid A; TRAPS, tumour necrosis factor receptor associated periodic syndrome
Comments	[a] MKD is also known as hyperimmunoglobulinemia D syndrome (HIDS). [b] Part 2 was week 1 to 16 and part 3 was week 16 to 40. [c] Persistent baseline flare was defined as a PGA score of 2 or more, or CRP level of more than 10 mg/l with less than 40% reduction from baseline. [d] Resolution was defined as a PGA score of less than 2 plus CRP level of 10 mg/l or less or a reduction by 70% or more from baseline. [e] Flare was defined as a PGA score of 2 or more and CRP level of 30 mg/l or more that occurred after resolution of index flare.
Source of funding	Novartis

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clearly described in the paper and supplementary paper.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Data reported and analysed appropriately to support conclusions.
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria may reduce this. This includes only recruiting people with cr-FMF.
Total	9/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 5 Arostegui et al. (2017)

Study reference	Arostegui J I, Anton J, Calvo I et al. (2017) Open-Label, Phase II Study to Assess the Efficacy and Safety of Canakinumab Treatment in Active Hyperimmunoglobulinemia D With Periodic Fever Syndrome. Arthritis & rheumatology 69(8): 1679–1688
Unique identifier	NCT01303380, EudraCT2010-020904-31
Study type (and NSF-LTC study code)	Open-label phase 2 study P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of canakinumab treatment in active HIDS with periodic fever syndrome.
Study dates	2011 to 2014.
Setting	3 medical centres in Spain (2 paediatric centres and 1 adult centre)

Number of participants	N=9
Population	Participants with HIDS were on average 16 years (range 5.4 to 29.2 years) and 67% were female. Six of the participants were children. The participants with HIDS on average had approximately 20 episodes reported annually before the study. Most (8/9) of the participants were Caucasians. Previous administered treatments include, NSAIDs, colchicine, antibiotics, corticosteroids, etanercept and anakinra.
Inclusion criteria	Participants: • aged 2 years or more at baseline • HIDS diagnosis confirmed by the identification of biallelic MVK mutations • with active HIDS[a] at the start of canakinumab treatment • who have a history of 3 or more inflammatory episodes with each episode lasting 4 or more days and limiting normal daily activities in the historical period[b]
Exclusion criteria	Participants: • who were pregnant or nursing • on concomitant treatment with other investigational medicines during the 30 days before enrolment • with history of recurrent infections and/or evidence of active infection • who have received a live-virus vaccination within 3 months before the start of the study start • with positive test for TB at baseline or 2 months before baseline • who are immunocompromised for example positive test for HIV, hepatitis B or hepatitis C • who have a history of malignancy of any organ, treated or untreated, within the preceding 5 years
Intervention(s)	<u>Treatment period (period 1)</u> Participants received canakinumab 300 mg (or 4 mg/kg if weight 40 kg or less) subcutaneously once every 6 weeks during the treatment period (6 months). An additional dose of 150 mg (or 2 mg/kg if weight 40 kg or less) was given to participants who experienced a flare[a] before week 4 who then went on to receive 450 mg (or 6 mg/kg if weight 40 kg or less) of canakinumab every 6 weeks starting at week 6[c]. <u>Withdrawal period (period 2)</u> During this 6 month period canakinumab was only given to participants who experienced a disease flare[a]. <u>Extension period (period 3)</u> The same dose of canakinumab was given to participants as for the treatment period.
Comparator(s)	None

Length of follow-up	6 month treatment period, followed by a withdrawal period lasting up to 6 months and a 24-month extension period.
Outcomes	Primary outcome: • Reduction in the frequency of attacks[a] during the treatment period compared with historical period[b] (number of attacks per participant).
	Secondary outcomes: • Recurrence of attacks[a] during period 1 and period 3 • Changes in the attack severity score[d] • Changes in the activity of 4 key HIDS features (fever, lymphadenopathies, apthous ulcers and pain) • Control of HIDS[e] • Changes in CRP level overtime • Time to resolution[f] of attack after the first canakinumab dose • Need for canakinumab dose adjustments and/or rescue medicines[c]
	Safety outcomes: • Adverse events • Serious adverse events • Discontinuations
Abbreviations	CRP, C-reactive protein; HIDS, hyperimmunoglobulinemia D; PGA, physician's global assessment
Comments	[a] PGA score of 2 or more and CRP of more than 10 mg/l. [b] Historical period was defined as the most recent 6 months in which the participants did not receive treatment for HIDS other than symptomatic treatment with NSAIDs and//or corticosteroids. [c] Participants who experienced a flare between weeks 5 and 6 received rescue medication (NSAIDs or corticosteroids, 0.5 mg/kg for 3 days) and waited up to week 6 to receive canakinumab. [d] Attack severity score was defined by the physician's and participants global assessments of disease activity based on a 5-point scale (0=absent signs/symptoms, 1=minimal, 2=mild, 3=moderate, 4=severe disease activity). [e] Control was assessed by physicians and participants during periods 1 and 2 and ever 12 weeks during period 3, based on a 5-point scale (0=no control of HIDS-associated signs and symptoms since last visit, 1=poor control, 2=some control, 3=good control, 4=excellent control) [f] Complete response was defined as a PGA score of 1 or less and a CRP level of less than 10 mg/l.
Source of funding	Novartis

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	This was an open-label and non-randomised study therefore the design of the study and use of clinical judgement to assess the primary endpoint are known to be susceptible to bias. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution.
3. Are the methods clearly described?	1/2	The methods are described for the intervention, However, there is no further information on methods for handling bias, and confounding.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The study was open-label and uncontrolled, and subject to bias and confounding. The data are not adequate to support firm conclusions.
5. Are the results generalisable?	1/2	The results are generalisable to the decision problem. However, the study includes only 9 participants, most being children.
Total	6/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 6 Brik et al. (2014)

Study reference	Brik R, Butbul-Aviel Y, Lubin S et al. (2014) Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single arm pilot study. Arthritis & rheumatology 66 (11): 3241–3
Unique identifier	NCT01148797

Study type (and NSF-LTC study code)	Open-label phase 2 study P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of canakinumab in the treatment of children with cr-FMF.
Study dates	December 2010 to February 2012
Setting	2 centres in Israel
Number of participants	N=7
Population	7 Caucasian children with FMF (5 boys and 2 girls) with median age 9.5 years (range 6.8 to 14.9 years).
Inclusion criteria	Children with cr-FMF were included if the diagnosis was confirmed by Tel-Hashomer diagnostic criteria, with 2 exon 10 mutations on the MEFW exon 10 gene. All children were colchicine-resistant having had 3 or more well-documented acute FMF attacks during the 3 months before screening despite treatment with colchicine at 1–2 mg or more per day (based on age) for at least 3 months.
Exclusion criteria	Excluded participants: • with end-organ dysfunction because of amyloidosis • taking oral or intravenous steroids within 1 month before baseline • taking steroids for reasons other than FMF • with presence or history of any other inflammatory rheumatic disease • with an active non-infective gastrointestinal disease, a chronic or acute renal or hepatic disorder, or a significant coagulation defect • with a positive protein-derivative test when a latent or active TB infection cannot be excluded • with a positive HI) status or current (acute or chronic) hepatitis B or C • who are pregnant or nursing • with any active or chronic infection or any major episode of infection requiring hospitalisation or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days before screening • with malignancy, except for successfully excised squamous or basal cell carcinoma of the skin • who have received a live-virus vaccine within 3 months before baseline visit Taken from clinicaltrials.gov: NCT01148797

Intervention(s)	Three subcutaneous injections of canakinumab 2 mg/kg (maximum 150 mg) were administered 4 weeks apart. The first dose (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). Note: Daily colchicine treatment was also given at the usual dose.
Comparator(s)	None
Length of follow-up	6 month study: treatment period was day 1 to 86, post-treatment period was after day 86 when participants were followed up for another 2 visits that occurred between day 126 and 160, or until an attack[a] occurred (which ever occurred first).
Outcomes	Primary outcome: • Proportion of participants with 50% or more reduction in the frequency of FMF attacks during the treatment period compared with the pre-treatment period[b], Secondary outcomes: • Acute-phase reactant levels • Health-related quality of life (Child Health Questionnaire—Parent Form 50 [CHQ-PF50]) • Physician's global assessment of FMF control • Time to attack following the last canakinumab injection (day 57) Safety outcomes: • Adverse events • Serious adverse events • Discontinuations
Abbreviations	cr-FMF, colchicine-resistant familial Mediterranean fever
Comments	[a] Attacks were then treated with paracetamol and/or non-steroidal anti-inflammatory drugs only. [b] There was no clear definition of 'attack' reported in the study.
Source of funding	Novartis

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	This was an open-label and non-randomised study therefore the design of the study and use of clinical judgement to assess the primary endpoint are known to be

		susceptible to bias. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution.
3. Are the methods clearly described?	1/2	The methods are described for the intervention, However, there is no further information on methods for handling bias, and confounding and for calculating sample size.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The study was open-label and uncontrolled, and subject to bias and confounding. The data are not adequate to support firm conclusions.
5. Are the results generalisable?	1/2	The results are generalisable to the decision problem. However, the study includes only 7 participants which were children only.
Total	6/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 7 Gattorno et al. (2017)

Study reference	Gattorno M, Obici L, Cattalini M et al. (2017) Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. Annals of the rheumatic diseases 76(1): 173–178
Unique identifier	NCT01242813
Study type (and NSF-LTC study code)	Open-label phase 2 study P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of canakinumab in inducing complete or almost complete responses within 15 days after the first dose in people with active TRAPS.
Study dates	October 2010 to June 2014
Setting	Multicentre study conducted in England (1 centre), Ireland (1 centre) and Italy (4 centres).
Number of participants	N=20

Population	People with TRAPS had a mean age of 34 years (6 participants were less than 18 years of age), 95% were white and 65% were male. Nine participants had relapsing TRAPS and 11 were reported to have chronic TRAPS. The number of episodes per year were reported to be a mean of 9.9 and episodes lasted for a mean of 11.9 days. The PGA of TRAPS activity was reported to be mild (score of 2) in 65%, moderate (score of 3) in 30% and severe (score of 4) in 5% of the participants. Three participants had amyloid A amyloidosis. Overall, 19 patients received prior TRAPS treatment with anakinra (65%), etanercept (30%), glucocorticoids (50%) and NSAIDS (15%) which were discontinued before study entry.
Inclusion criteria	Participants with : • a diagnosis of TRAPS and a mutation of TNFRSF1A gene • at least 4 years of age at the time of the screening visit • a diagnosis of recurrent TRAPS experiencing more than 6 episodes per year before receiving an effective biologic therapy and the duration of each episode lasting at least 8 days Participants who have been treated with anakinra must have demonstrated a partial or complete clinical response with an associated decrease in their inflammation markers (CRP and SAA). Participants with active TRAPS who have symptoms (skin disease extremity musculoskeletal pain, abdominal pain and eye manifestations) of active TRAPS (PGA of 2 or more) and an elevated CRP of more than 10 mg/l and/or SAA of more than 10 mg/l at the time of first canakinumab treatment.
Exclusion criteria	Participants who: • are pregnant or nursing (lactating) • have a history of being immunocompromised, including a positive HIV test and positive tuberculosis screen • have had live vaccinations within 3 months before the start of the trial, during the trial, and up to 3 months following the last dose • have a history of significant other medical conditions, which in the investigator's opinion would exclude the patient from participating in this trial • have a history of recurrent and/or evidence of active bacterial, fungal, or viral infection(s) • have used prohibited therapies, any other investigational biologics within 8 weeks before the baseline visit • have a history of malignancy of any organ system (other than localised basal cell carcinoma of the skin), treated or untreated, within the past 5 years See study protocol for more details
Intervention(s)	Participants weighing 40 kg or more received canakinumab 150 mg subcutaneously once every 4 weeks during the treatment period (days 1, 29, 57 and 85). A single dose up-titration to 300 mg was

	allowed at day 8 in non-responders at the discretion of the treating physician. Participants weighing 40 kg or less received canakinumab 2 mg/kg once every 4 weeks, with a single dose up-titration to 4 mg/kg allowed for non-responders at day 8. Participants who relapsed during the follow-up period received another dose of canakinumab equivalent to the last dose received.
Comparator(s)	None
Length of follow-up	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. Participants 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.
Outcomes	Primary outcome: • Proportion of participants with active TRAPS achieving complete[a,b] or almost complete[c] response at day 15
	Secondary outcomes: • Proportion of participants with: - complete or almost complete response at day 8 - clinical remission (PGA score of 1 or less) at days 8 and 15 - serological remission (CRP and SAA of 10 mg/l or less) at days 8 and 15 • Time to the investigator's assessment of clinical remission[d] • Time to relapse[d] in the withdrawal phase • Health-related quality of life (exploratory)
	Safety outcomes: • Adverse events • Serious adverse events
Abbreviations	CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drugs; PGA, physician's global assessment; SAA, serum amyloid A; TRAPS, tumour necrosis factor receptor associated periodic syndrome
Comments	[a] Complete response was defined as clinical remission (PGA score 1 or less) with full serological remission (CRP less than 10 mg/l and/or SAA less than 10 mg/l). [b] In patients with a stable complete response, corticosteroid doses could be reduced at the investigators discretion from day 29 for complete responders only. [c] Almost complete response was defined as clinical remission with partial serological remission (70% or more reduction of baseline CRP and/or SAA). [d] Relapse was defined as a PGA score of 2 or more and represents an increase by 1 or more point from day 15 and CRP and/or SAA of 30 mg/l or more without other explanation for cause and represents a 30% increase from day 15.
Source of funding	Novartis

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	This was an open-label and non-randomised study therefore the design of the study and use of clinical judgement to assess the primary endpoint are known to be susceptible to bias. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution.
3. Are the methods clearly described?	1/2	The methods are clearly described for the intervention, However, there is no further information on methods for handling bias, and confounding and for calculating sample size.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The study was open-label and uncontrolled, and subject to bias and confounding. The data are not adequate to support firm conclusions.
5. Are the results generalisable?	1/2	The results are generalisable to the decision problem. However, the study includes only 20 participants.
Total	6/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 8 Gul et al. (2015)

Study reference	Gul A, Ozdogan H, Erer B et al. (2015) Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. Arthritis research & therapy 17: 243
Unique identifier	NCT01088880
Study type (and NSF-LTC study code)	Open-label phase 2 study P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of canakinumab in adolescents and adults with FMF, who are resistant or intolerant to higher doses of colchicine.
Study dates	April 2010 to August 2011
Setting	Medical centre in Turkey
Number of participants	N=9
Population	Participants with FMF intolerant to colchicine had a median age of 22 years (range 12 to 34 years) and 77.8% were female. The time-adjusted attack frequency[a] was reported to be 3.29 (2.47 to 4.2). All of the participants were on colchicine treatment (n=2, 1.5 mg/day and n=7, 2 mg/day).
Inclusion criteria	Participants had a typical type I phenotype, fulfilling the criteria for FMF diagnosis (Tel-Hashomer diagnostic criteria), along with at least one of the exon 10 mutations in the MEFV gene. Colchicine-compliant participants with a history of 1 or more attacks per month within 3 months before the screening were eligible to enter the first 30-day run-in period. Participants who had at least 1 attack during that period advanced to a second 30-day period. Participants who are intolerant to effective doses of colchicine (1.5 to 2 mg/day).
Exclusion criteria	Participants with end-organ dysfunction because of secondary amyloidosis, active tuberculosis or any other infectious diseases, or a history of malignancy within the last 5 years were excluded from the study.
Intervention(s)	Participants received a total of 3 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[b].
Comparator(s)	None
Length of follow-up	12-week treatment period and followed up to 2 months or until the next attack.
Outcomes	Primary outcome: • Proportion of participants with 50% or more reduction in time-adjusted frequency of attacks[a,c]

	Secondary outcomes: • Percentage of participants 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) • CRP and SAA levels • Physicians' and patients' global assessments of control of FMF since the last visit
	Safety outcomes: • Adverse events • Discontinuations
Abbreviations	CRP, C-reactive protein; FMF, familial Mediterranean fever; SAA, serum amyloid A
Comments	[a] Time-adjusted attack frequency/84 days observed in screening and run-in up to and including baseline attack. Because of the unequal pre-treatment and treatment periods, attack rates were adjusted to the 84-day treatment period compared with the pre-treatment periods. [b] Stable doses of colchicine (1.5 to 2 mg/day) were allowed throughout the study without any dose modification, and compliance was reported to be followed tightly throughout the study. [c] FMF attacks were confirmed by presence of fever, clinical findings of serositis/arthritis, and elevated CRP levels. Details of each attack (duration, type, severity, maximum body temperature) were recorded in diaries.
Source of funding	Novartis

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	This was an open-label and non-randomised study therefore the design of the study and use of clinical judgement to assess the primary endpoint are known to be susceptible to bias. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution.

3. Are the methods clearly described?	1/2	The methods are described for the intervention, However, there is no further information on methods for handling bias, and confounding.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The study was open-label and uncontrolled, and subject to bias and confounding. The data are not adequate to support firm conclusions.
5. Are the results generalisable?	1/2	The results are generalisable to the decision problem. However, the study includes only 9 participants, most being female.
Total	6/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Appendix 4 Results tables

Table 9 De Benedetti et al. (2018)

	TRAPS		MKD[a]		Cr-FMF	
	Canakinu-mab[b]	**Placebo**	**Canakinu-mab[b]**	**Placebo**	**Canakinu-mab[b]**	**Placebo**
Primary outcome[c]						
N	**22**	**24**	**37**	**35**	**31**	**32**
Proportion of participants who achieved complete response[d]	45.5% (10/22)	8.3% (2/24)	35.1% (13/37)	5.7% (2/35)	61.3% (19/31)	6.3% (2/32)
	OR 9.17 (95% CI 1.51 to 94.6) p=0.0065[e]		OR 8.94 (95% CI 1.72 to 86.4) p=0.0030[e]		OR 23.8 (95% CI 4.38 to 227.5) p<0.001[e]	
Secondary outcomes						
Proportion of participants at week 16 with a PGA score of less than 2	45.5% (10/22)	4.2% (1/24)	46% (17/37)	5.7% (2/35)	64.5% (20/31)	9.4% (3/32)
	OR 23.8 (95% CI 2.52 to 224.9) p=0.0057[f]		OR 13.6 (95% CI 2.83 to 65.6) p=0.0011[f]		OR 17.0 (95% CI 4.15 to 69.2) p<0.0001f	
Proportion of participants at week 16 with a CRP level of 10 mg/l or less	36.4% (8/22)	8.3% (2/24)	40.5% (15/37)	5.7% (2/35)	67.7% (21/31)	6.3% (2/32)
	OR 6.64 (95% CI 1.20 to 36.6) p=0.0298[f]		OR 12.7 (95% CI 2.53 to 63.9) p=0.0020f		OR 29.8 (95% CI 5.86 to 151.3) p<0.0001[f]	
Proportion of participants at week 16 with a SAA level of 10 mg/l or less	27.3% (6/22)	0% (0/24)	13.5% (5/37)	2.9% (1/35)	25.8% (8/31)	0% (0/32)
	OR 16.7 (95% CI 1.04 to 268.5) p=0.0471[f]		OR 5.26 (95% CI 0.53 to 52.0) p=0.1555		OR 17.5 (95% CI 0.92 to 332.9) p=0.572	
Proportion of participants receiving canakinumab or placebo every 8 weeks who had no new flare up to week 40[g]	75% (3/4)	40% (2/5)	50% (3/6)	14.3% (1/7)	77.8% (7/9)	30% (3/10)
	P=0.52		No p-value		No p-value	
Proportion of participants with resolution of baseline flare at day 15[h]	64% (14/22)	21% (5/24)	65% (24/37)	37% (13/35)	81% (25/31)	31% (10/32)
Proportion of participants who needed an additional dose of canakinumab[i]	50% (11/22)	n/a	51.4% (19/37)	n/a	32.3% (10/31)	n/a

	TRAPS		MKD		Cr-FMF	
	Canakinu-mab[b] up to 40 weeks (normalised to 1 year)	12 months before baseline	Canakinu-mab[b] up to 40 weeks (normalised to 1 year)	12 months before baseline	Canakinu-mab[b] up to 40 weeks (normalised to 1 year)	12 months before baseline
Frequency of attacks	N=16		N=21		N=16	
	1.2	10.1	2	13.7	1.2	32.5
	TRAPS		MKD		Cr-FMF	
	Canakinu-mab[b]	Baseline	Canakinu-mab[b]	Baseline	Canakinu-mab[b]	Baseline
[redacted]						
[redacted]						
[redacted]						
[redacted]						
Safety outcomes[m]						
	Combined placebo[n]	TRAPS		MKD[a]		cr-FMF
Exposure, patient-years	8	12.1		19.1		16.4
Adverse events						
Including fever and disease flare	136	112		251		134
Excluding fever and disease flare	114	111		243		126
Infections	19	26		72		28
Non-infectious adverse events[o]	23	17		45		33
Serious adverse events						
Including disease flare	8	3		11		7
Excluding disease flare	6	3		8		7
Infections	2	0		4		1

Other				
Discontinuations	0	2[p]	2[q]	0

[a] MKD is also known as hyperimmunoglobulinemia D syndrome (HIDS)

[b] Intervention was subcutaneous canakinumab 150 mg (2 mg/kg for weight 40 kg or less) every 4 weeks, option to up-titrate to 300 mg (4 mg/kg if weight 40 kg or less) every 4 weeks in part 2

[c] Full analysis set included all randomised participants in the randomised treatment part

[d] Defined as resolution of baseline flare at day 15 (PGA score of less than 2 plus CRP level of 10 mg/l or less or a reduction by 70% or more from baseline) and no new flare (PGA score of 2 or more and CRP level of 30 mg/l or more that occurred after resolution of index flare)

[e] Indicates statistical significance (two-sided) at the 0.05 level based on Fisher exact test

[f] Indicates statistical significance (two-sided) at the 0.05 level based on the logistic regression model with treatment group and baseline PGA, CRP or SAA as explanatory variables for each cohort

[g] Participants in the canakinumab group who met the primary outcome in part 2 underwent a second randomisation at week 16 to receive 150 mg of canakinumab or placebo every 8 weeks (open-label part 3)

[h] Resolution of baseline flare was defined as a PGA of 2 or less, and CRP of 10 mg/l or less or reduction of 70% or more from baseline

[i] The blinded dose increase consisted of one add-on injection of 150 mg of canakinumab every 4 weeks· if participants had a persistent baseline flare between days 8 and 14 (PGA score of 2 or more, or CRP level of more than 10 mg/l with less than 40% reduction from baseline) or a lack of resolution at day 15[h]

[j] The CHQ-PF50 was used to assess the impact of cr-FMF, HIDS/MKD, or TRAPS disease on the child's health-related QoL from the perspective of the parent. An increase from baseline of 2, 5, and 8 points in the CHQ-PF50 physical and psychological component summary scores corresponds to a small, moderate and large treatment effect, respectively

[k] Scores for participants who remained on canakinumab 150 mg every 4 weeks at week 17 (part 2)

[l] SF-12 measures the impact of disease on overall QoL An increase from baseline of 3, 5, and 8 points in the SF-12 physical and mental component summary scores corresponds to a small, moderate and large treatment effect, respectively.

[m] Safety set analysis that included participants exposed to at least 1 dose of canakinumab in part 2 (up to week 16). The study listed adverse events with at least 20 occurrences. Note full results are available in the study paper for adverse events in cumulative part 2 and part 3

[n] Includes the participants in all 3 cohorts who were randomly assigned to placebo at baseline

[o] Includes most common events: abdominal pain, headache, diarrhoea, arthralgia and injection-site reaction

[p] During part 3, 1 participant had grade 2 neutropenia, which was considered by the investigator to be related to canakinumab and resolved in 5 days, and 1 had a mild reduction in the glomerular filtration rate, which was considered to be unrelated to the canakinumab)

[p] During part 2, 1 participant had a disease flare, and 1 had an event of pericarditis

Abbreviations

CHQ-PF50, child health questionnaire – parent form 50; CI. confidence interval; CRP, c-reactive protein; cr-FMF, colchicine-resistant familial Mediterranean fever; MKD, mevalonate kinase deficiency; OR, odds ratio; PCS, physical component summary; PsS, psychological component summary; PGA, physician's global assessment; QoL, quality of life; SAA, serum amyloid A; SF-12, short-form-12 health survey; TRAPS, tumour necrosis factor receptor associated periodic syndrome

Table 10 Arostegui et al. (2017)

	Historical period[a]	Canakinumab[b]	Analysis
Primary outcome			
N	**9**	**9**	
Median number of attacks[c] per participant	5 (range 3 to 12 attacks)	0 (range 0 to 2 attacks)[d,e]	p=0.009
Secondary outcomes			
Recurrence of attacks[c]	9/9	Treatment period: 2/9 Period 3[f]: 4/8[g]	N/a
Changes in the attack severity score[h]	At baseline flare: Mild in 5/9 attacks Moderate in 4/9 attacks	Period 1 (treatment period): Mild in 1/2 attacks Moderate in 1/2 attacks Period 3: Mild in 5/8 attacks Minimal signs/symptoms reported in 2/8 attacks 1/8 without signs/symptoms	
Control[i] of HIDS (PGA)	No disease control 66.7% (6/9) Poor disease control 33.3% (3/9)	Good 44.4% (4/9)[j] Excellent 55.6% (5/9)[j]	
Median CRP level	117.7 mg/l (range 23 to 165 mg/l)	0.8 mg/l (range 0 to 6 mg/l)[k]	
Median time to resolution of attack after the first canakinumab dose	n/a	3 days (range 1 to 5 days)	
Need for canakinumab dose adjustments and/or rescue medicines[l]	n/a	2/9 needed additional canakinumab dose because of relapse during treatment period and 1 of these participants received rescue medicine	
Safety outcomes			
Number of non-serious adverse events	n/a	84 (n=9)[m]	n/a

	Historical period[a]	Canakinumab[b]	Analysis
Serious adverse events	n/a	14 (n=4)[n]	
Discontinuations because of adverse events	n/a	0	

[a] Historical period was defined as the most recent 6 months in which the participants did not receive treatment for HIDS other than symptomatic treatment with NSAIDs and//or corticosteroids.

[b] 300 mg (or 4 mg/kg if weight 40 kg or less) subcutaneously every 6 weeks with option to titrate to 450 mg (or 6 mg/kg if weight 40 kg or less) every 6 weeks.

[c] Attack/flare was defined as a PGA score of 2 or more and CRP of more than 10 mg/l

[d] During the withdrawal period (period 2) 7/9 experienced an attack and during the 24-monthe extension (period 3) the median number of attacks per participant was 0 (range 0 to 4 attacks) (total of 8 attacks reported).

[e] Treatment period was 6 months.

[f] Period 3 was the 24-month extension period.

[g] Eight of the 9 participants completed period 3.

[h] Attack severity score was defined by the physician's and participants global assessments of disease activity based on a 5-point scale (0=absent signs/symptoms, 1=minimal, 2=mild, 3=moderate, 4=severe disease activity).

[i] Control was assessed by PGA during periods 1 and 2 and ever 12 weeks during period 3, based on a 5-point scale (0=no control of HIDS-associated signs and symptoms since last visit, 1=poor control, 2=some control, 3=good control, 4=excellent control).

[j] Results reported at the end of treatment period (period 1). At the end of period 3, 8 participants rated the control as being excellent.

[k] At day 15 of treatment period.

[l] Participants who experienced a flare between weeks 5 and 6 received rescue medication (NSAIDs or corticosteroids, 0.5 mg/kg for 3 days) and waited up to week 6 to receive canakinumab.

[m] An adverse event of fungal vaginitis was thought to be related to canakinumab. Most frequent were related to suspected infections (43.9%) that often needed treatment with systemic antibiotics. The physician rated them all to be mild in intensity except for 1 non-serious adverse event of cellulitis being rated as moderate.

[n] Six were reported to be mild in intensity, 5 were moderate and 3 were severe. Eight of these serious adverse events occurred in the same participant who experienced acute peritonitis, anaemia, bacteraemia, gastrointestinal bleeding, hypertensive crisis, pneumonia, severe anaemia and volume overload. This participant had systemic amyloid A amyloidosis, kidney transplant, digestive haemorrhage, hypertension and chronic anaemia and needed peritoneal dialysis. One participant experienced hidradenitis suppurativa requiring hospitalisation and another developed cellulitis.

Abbreviations

CRP, C-reactive protein; HIDS, hyperimmunoglobulinemia D; PGA, physician's global assessment

Table 11 Brik et al. (2014)

	Baseline	Canakinumab[a]
Primary outcome		
N	**7**	**7**

	Baseline	Canakinumab[a]
Proportion of participants with 50% or more reduction in the frequency of FMF attacks during the treatment period[b]	Not reported	85.7% (range 76% to 100%) (6/7)
Secondary outcomes		
Median acute-phase reactant levels	CRP: 74 mg/l SAA: more than 500 mg/l	CRP at day 8: 2 mg/L and at day 86, 1.3 mg/l SAA at day 57: 2.5 mg/l and at day 86, 12.2 mg/l
Health-related quality of life (CHQ-PF50)	Physical domain: median score of 21 Psychosocial domain: median score of 31	Physical domain: median score of 46 at day 86 Psychosocial domain: median score of 40 at day 86
Physician's global assessment of FMF control	Rated very poor in 3/7, poor in 3/7 and fair in 1/7	At day 86, rated very good in 4/7 and good in 3/7
Time to attack following the last canakinumab injection (day 57)	Not reported	Median 25 days (range 5 to 34 days)
Safety outcomes		
Adverse events	n/a	11 events[c] in 4/7
Serious adverse events[d]	n/a	0
Deaths	n/a	0
Discontinuations	n/a	0

[a] Intervention was subcutaneous canakinumab 150 mg (2 mg/kg for weight 40 kg or less) every 4 weeks, option to up-titrate to 300 mg (4 mg/kg if weight 40 kg or less) every 4 weeks.

[b] Treatment period was day 1 to 86.

[c] Reported to be mild except for 1 moderate streptococcal throat infection. Two of these were infections.

[d] Such as opportunistic infections or malignancies,

Abbreviations

CHQ-PF50, Child Health Questionnaire-Parent Form 50; CRP, C-reactive protein; cr-FMF, colchicine-resistant familial Mediterranean fever; SAA, serum amyloid A

Table 12 Gattorno et al. (2017)

	Canakinumab[a]
Primary outcome	
N	**20**
Proportion of participants with active TRAPS achieving complete[b] or almost complete[c] response at day 15[d]	19/20 (95%,95% CI 75.1% to 99.9%)

	Canakinumab[a]
Secondary outcomes	
Proportion of participants with clinical remission[e] at day 15[f]	100% (20/20)
Proportion of participants with serological remission[g] at day 15[h]	60% (12/20)
Median time to clinical remission[i]	4 days (95% CI 3 to 8 days)
Median time to relapse[j] in the withdrawal phase[k] following last canakinumab dose	91.5 days (95% CI 65 to 117 days)
Health-related quality of life[l]	**For participants 18 years or over:** The mean physical component summary score was 41.8 at baseline, 49.3 at day 15 and 51.4 at day 113. The mean mental component summary score was 39.3 at baseline, 46.6 at day 15 and 49.0 at day 113. **For the paediatric participants (n=5):** The mean physical health score was 35.4 at baseline, and more than 40 at day 15 and day 113. The mean psychosocial score was 52.7 at baseline and was reported to be more than 50 throughout the study, except on days 365 and 617, they were noted at 46.6 and 47.2, respectively.
Safety outcomes[m]	
Adverse events	100% (20/20)[n]
Serious adverse events	35% (7/20)[o]

[a] Intervention was subcutaneous canakinumab 150 mg (2 mg/kg for weight 40 kg or less) every 4 weeks, option of a single up-titration to 300 mg (4 mg/kg if weight 40 kg or less) every 4 weeks at day 8

[b] Complete response was defined as clinical remission (PGA score 1 or less) with full serological remission (CRP less than 10 mg/l and/or SAA less than 10 mg/l).

[c] Almost complete response was defined as clinical remission with partial serological remission (70% or more reduction of baseline CRP and/or SAA).

[d] At day 8, 80% (16/20) achieved this outcome (secondary outcome). Up-titration to 300 mg or 4 mg/kg for weight 40 mg or less, was given to 2 out of 4 non-responders (defined as no change or worsening from baseline PGA score and/or increased or less than 50% reduction from baseline CRP and/or SAA) at day 8. The same 2 achieved a complete or almost complete response by day 15. The remaining 2 who did not receive an up-titration still achieved a complete or almost complete response at day 15.

[e] Clinical remission was defined as a PGA score 1 or less with full serological remission (CRP less than 10 mg/l and/or SAA less than 10 mg/l)

[f] At day 8, 55% (11/20) achieved this secondary outcome.

[g] Serological remission was defined as CRP and SAA of 10 mg/l or less.

[h] At day 8, 35% participants were in serological remission.

[i] Assessed by the investigator.

[j] Relapse was defined as a PGA score of 2 or more and represents an increase by 1 or more point from day 15 and CRP and/or SAA of 30 mg/l or more without other

	Canakinumab[a]
explanation for cause and represents a 30% increase from day 15. All 20 participants relapsed (11 mild, 7 moderate and 2 severe) during the withdrawal/follow-p period. [k] The withdrawal/follow-up period lasted up to 5 months after the 4 month treatment period. [l] This was an exploratory objective. Participants 18 years or more completed the medical outcomes study 36-Item short-form health survey (SF-36) at baseline, and those less than 18 years completed the child health questionnaire (CHQ-PF50). Neither of these tools has been validated for use in TRAPS. Participants completed HRQoL questionnaires on days 1, 15, 113, 253 and then every 12 weeks during long-term treatment. [m] Recorded during 33 months of the study. [n] All participants reported at least 1 adverse event that included nasopharyngitis (60%), abdominal pain (55%), headache (55%), oropharyngeal pain (55%) and fever (50%). Most of the adverse events were reported to be mild to moderate. [o]Serious adverse events included pericarditis, abdominal pain, diarrhoea, intestinal obstruction, vomiting, upper respiratory tract infection, meniscus injury, hypertriglyceridaemia, hyperkalemia, pregnancy-related condition (wife of enrolled participant became pregnant), foot deformity and condition became aggravated.	
Abbreviations CRP, C-reactive protein; PGA, physician's global assessment; SAA, serum amyloid A; TRAPS, tumour necrosis factor receptor associated periodic syndrome	

Table 13 Gul et al. (2015)

	Baseline	Canakinumab[a]
Primary outcome		
N	**9**	**9**
Proportion of participants with 50% or more reduction in time-adjusted frequency of attacks[b,c]	n/a	100% (9/9)[d]
Secondary outcomes		
Percentage of participants with no attacks in the treatment period	n/a	88.9% (8/9)[e]
Median time to next attack after the last canakinumab administration	n/a	71 days (range 31 to 78 days)[f] n=5
Quality of life assessed by the 36-item short-form health survey (median score)	Physical score: approximately 30 Mental score: approximately 39	Treatment period (at day 86): Physical score: approximately 90 Mental score: approximately 90 End of study: Physical and mental scores were both approximately between 70 and 80 at the end of the study

Median CRP level[g]	58 mg/l	0.9 mg/l (treatment period at day 86)
Median SAA level[h]	162 mg/l	9.69 mg/l[i] (treatment period at day 86)
Physician's and patient's global assessment of control of FMF since the last visit	Poor; 8/9 Fair: 1/9	Treatment period (at day 86): Good: 1/9 Very good: 8/9 End of study Fair: 1/9 Good: 1/9 Very good: 7/9
Safety outcomes		
Number of participants reporting at least 1 adverse event	n/a	88.9% (8/9)[j]
Discontinuations	n/a	0

[a] Canakinumab 150 mg was administered subcutaneously at 4-week intervals during the 12-week treatment period. No participant qualified for a dose increase between the first and second dose.

[b] Time-adjusted attack frequency/84 days observed in screening and run-in up to and including baseline attack. Because of the unequal pre-treatment and treatment periods, attack rates were adjusted to the 84-day treatment period compared with the pre-treatment periods.

[c] FMF attacks were confirmed by presence of fever, clinical findings of serositis/arthritis, and elevated CRP levels. Details of each attack (duration, type, severity, maximum body temperature) were recorded in diaries.

[d] Severity of attack was reported to be very severe (n=5) and severe (n=4) at baseline compared with very severe (n=1) during treatment period. At follow-up, 4/9 had no attack and the other participants who had attacks reported them to be mild (n=1), moderate (n=2), severe (n=1) and very severe (n=1). Severity of attack was assessed according to participant's assessment according to previous experiences.

[e] During the treatment period, only 1 participant, who was receiving 2 mg/day colchicine, had an attack of peritonitis on day 54.

[f] During the 2 month follow-up period.

[g] Normal CRP level is 0 to 10 mg/l

[h] Normal SAA level is 10 mg/l

[i] n=8

[j] Headache (n=4) and upper respiratory tract infection (n=2) were the only adverse events reported by more than 1 participant. All adverse events were mild or moderate except 1, which was a severe headache

Abbreviations

CRP, C-reactive protein; FMF, familial Mediterranean fever; SAA, serum amyloid A;

Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.

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