EMA/881775/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment Report

ILARIS

International non-proprietary name: canakinumab

Procedure No. EMEA/H/C/001109/II/0075

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	14 Aug 2021	14 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	08 Oct 2021	08 Oct 2021	☐
☐	PRAC Rapporteur Assessment Report	15 Oct 2021	15 Oct 2021	☐
☐	CHMP Co-Rapporteur Critique	20 Oct 2021	20 Oct 2021	☐
☐	PRAC members comments	20 Oct 2021	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Oct 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	28 Oct 2021	28 Oct 2021	☐
☐	CHMP members comments	29 Oct 2021	29 Oct 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	04 Nov 2021	04 Nov 2021	☐
☐	Request for supplementary information	11 Nov 2021	11 Nov 2021	☐
☐	Re-start of procedure	21 Mar 2022	21 Mar 2022	☐
☐	CHMP Rapporteur Assessment Report	19 Apr 2022	19 Apr 2022	☐
☐	PRAC Rapporteur Assessment Report	22 Apr 2022	n/a	☐
☐	PRAC members comments	26 Apr 2022	26 Apr 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	28 Apr 2022	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	05 May 2022	05 May 2022	☐
☐	CHMP members comments	10 May 2022	10 May 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 May 2022	12 May 2022	☐
☐	Request for supplementary information	19 May 2022	19 May 2022	☐
☐	Letter of withdrawal submission by MAH		26 Oct 2022	☐

Procedure resources	
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List of abbreviations

AE	Adverse event
AOSD	Adult-onset Still's Disease
CAPS	Cryopyrin-associated Periodic Syndrome
CCL2	CC-chemokine ligand 2
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
ESR	Erythrocyte sedimentation rate
EU	European Union
FMF	Familial Mediterranean Fever
HIDS	Hyper-immunoglobulin D Syndrome
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIT	Investigator-initiated trial
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-1R	Interleukin-1 receptor
IL-1Ra	Interleukin-1 receptor antagonist
MKD	Mevalonate Kinase Deficiency
NSAIDs	Non-steroidal anti-inflammatory drugs
PGA	Physician's Global Assessment
PK	Pharmacokinetics
Q4W	Every 4 weeks
Q8W	Every 8 weeks
r	Correlation coefficient
SAA	Serum amyloid A
SAE	Serious adverse event
s.c.	Subcutaneous
SCE	Summary of Clinical Efficacy
SchS	Schnitzler Syndrome
SD	Standard Deviation
SF-36	36-item short form health survey
SJIA	Systemic Juvenile Idiopathic Arthritis
TRAPS	Tumour necrosis Factor Receptor-associated Periodic Syndrome
ULN	Upper limit of normal

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 25 June 2021 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of of adult patients with Schnitzler syndrome for ILARIS; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 13.0 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

The Paediatric Committee granted a product specific waiver for canakinumab (Ilaris) (EMEA-000060-PIP09-20) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council The European Medicines Agency, for all subsets of the paediatric population and the mentioned condition(s) in accordance with Article 11(1) (b) of said Regulation, on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s)on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

N/A

Similarity

N/A

Derogation(s) of market exclusivity

N/A

Scientific advice

On 01-Sep-2020, Novartis consulted the Rapporteurs for canakinumab, Paul-Ehrlich Institut and the Finnish Medicines Agency, in a Simultaneous National Scientific Advice meeting regarding the acceptability of the clinical data from Study DDE03T, an extensive literature review and supportive safety data from the CAPS pooled data, Study GDE01T in AOSD, and Study M2301 were included to support registration of canakinumab in the treatment of patients with SchS.

2. Recommendations

Grounds for refusal

Amendments to the marketing authorisation

3. EPAR changes

4. Scientific discussion

4.1. Introduction

4.1.1. Problem statement

Disease or condition

Schnitzler Syndrome (SchS)

State the claimed the therapeutic indication

Ilaris is indicated for the treatment of adult patients with Schnitzler syndrome.

Posology as proposed by the applicant

The recommended dose of canakinumab for patients with Schnitzler syndrome is 150 mg administered every 8 weeks via subcutaneous injection.

If a satisfactory clinical response has not been achieved 7 days after start of treatment, a second dose of canakinumab 150 mg can be administered. Thereafter, the recommended dose is 300 mg administered every 8 weeks.

Epidemiology and risk factors, screening tools/prevention

According to Orphanet (www.orpha.net), the portal for rare diseases and orphan drugs, SchS (Orpha number: ORPHA:37748) is listed as a rare disease but the exact prevalence is unknown (<1 per 1,000,000).

Diagnosis of SchS is important to recognize due to its association with malignancy, which can impact the overall prognosis. The risk of developing lymphoproliferative disorders such as lymphoma, IgM myeloma or Waldenström's macroglobulinaemia is approximately 15-20% for patients with SchS, similar to that of patients who have monoclonal IgM gammopathy of unknown significance. Lymphoproliferative disorders typically develop more than 10 to 20 years after the beginning of the first signs of the syndrome in most cases and hence, patients diagnosed with SchS warrant long-term follow-up. Infrequently, patients diagnosed with SchS can also develop Amyloid A (AA) amyloidosis as a serious consequence in the long-term.

Aetiology and pathogenesis

The aetiology remains unclear. SchS is most likely an acquired rather than genetic auto-inflammatory disorder due to the late onset, lack of familial clustering and no recurrent genetic alterations have been identified in SchS.

The clinical phenotype of SchS closely resembles that of the hereditary fever syndrome CAPS, a rare inherited inflammatory disease associated with overproduction of IL-1. The first clue to the auto-inflammatory nature of SchS came from the high efficacy of treatment with anakinra, an anti-IL-1 receptor antagonist. Anakinra was tested in light of its efficacy in patients with CAPS and the clinical

similarities between SchS and CAPS, a monogenic auto-inflammatory disease caused by pathogenic variants in the NLRP3 gene. Saurat et al (1991) was the first to identify anti-IL-1 autoantibodies in SchS patients, and since then, others have described abnormal lipopolysaccharide induced inflammatory cytokine release, especially of IL-1β production in SchS patients' peripheral blood mononuclear cells (PBMC; Ryan et al 2008, Pizzirani et al 2009, Launay et al 2013, Masson Regnault et al 2020), suggesting the utility of anti-IL-1 targeted therapy for patients with SchS. Although the exact pathogenetic pathways of SchS are mostly unknown, promising biomarkers such as CCL2 to monitor disease activity have been identified and may assist to distinguish SchS from other related auto-inflammatory diseases (e.g., chronic urticaria, AOSD and CAPS).

Clinical presentation, diagnosis

Schnitzler syndrome (SchS) is a rare, chronic, systemic auto-inflammatory disease with an onset in adults in their fifth decade of life. Because of the varied symptoms, non-specific phenotype of SchS and unfamiliarity of many physicians with this rare syndrome, a diagnosis is usually delayed, with time to diagnosis often exceeding 5 years. Researchers believe that SchS is highly underdiagnosed, making it difficult to determine its true frequency in the general population. Diagnosis for SchS is based on the Lipsker diagnostic criteria (Lipsker et al 2001) and more recently on the validated Strasbourg diagnostic criteria (Simon et al 2013, Gusdorf et al 2017).

The first clinical signs of SchS are generally urticarial rash, mainly associated with recurrent fever or joint and/or bone pain. Skin symptoms are recurrent urticarial rashes presenting in all patients diagnosed with SchS, primarily affecting the trunk and the extremities. Elementary lesions consist of wheals, rose or red macules or gently raised papules or plaques, which resolve within 24 hours. The frequency and duration of the flares is variable and can be exacerbated by stress, infections, cold temperatures (i.e., during winter) or physical exercise. Skin biopsies have confirmed that the most typical skin finding is a neutrophilic urticarial dermatosis without vasculitis or dermal oedema.

Another clinical sign is recurrent fever where body temperature can rise above 40 °C. In a majority of patients, fever can usually present simultaneously with urticarial rash and joint and/or bone pain. Joint and/or bone pain occurs in about 40% of patients, mostly in the lower limbs. In addition, monoclonal gammopathy belonging to the immunoglobulin M (IgM) class or less often to the IgG class is a defining biological feature of the disease. IgM levels can remain stable or progressively increase at a rate of about 0.5 to 1 g/L/year (Lipsker 2010). Individual cases with biclonal gammopathy combining IgM and IgG or even IgA gammopathy has also been described. As a sign of generalized inflammation, laboratory parameters including acute phase reactants (CRP and serum amyloid A [SAA]) and erythrocyte sedimentation rate (ESR) are often elevated in patients with SchS. Overall, the disease follows a chronic course with considerable quality of life impairment, which can adversely affect an individual's social and professional life

Management

Currently, no approved treatment exists. Standard of care includes antihistamines, NSAIDs, systemic corticosteroids and other agents, which provide only partial or transient improvement of symptoms. Many patients remain symptomatic to a large degree, and this may have a strong impact on their day-to-day quality to life. Similarly, DMARDs are rarely useful in controlling symptoms of the disease. However, based on reports IL-1 inhibition appears to be an effective treatment for SchS with the majority of patients responding well to anakinra, an IL-1 receptor antagonist, or canakinumab.

4.1.2. About the product

Canakinumab (Ilaris®) is a high-affinity human monoclonal anti-human IL-1β antibody of the IgG1/κ isotype designed to functionally neutralize the bioactivity of this cytokine. IL-1β is recognized as one of the principal pro-inflammatory cytokines in a variety of inflammatory conditions, including periodic fever syndromes (including cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor receptor associated periodic syndrome, hyperimmunoglobulin D syndrome/mevalonate kinase deficiency, and familial Mediterranean fever), systemic juvenile idiopathic arthritis (SJIA), Adult-Onset Still's Disease (AOSD) and gouty arthritis for which canakinumab is currently approved for the treatment of these indications (approved indications vary depending on country).

4.1.3. The development programme/compliance with CHMP guidance/scientific advice

On 01-Sep-2020, Novartis consulted the Rapporteurs for canakinumab, Paul-Ehrlich Institut and the Finnish Medicines Agency, in a Simultaneous National Scientific Advice meeting regarding the acceptability of the clinical data from Study DDE03T, an extensive literature review and supportive safety data from the CAPS pooled data, Study GDE01T in AOSD, and Study M2301 were included to support registration of canakinumab in the treatment of patients with SchS.

The Paediatric Committee granted a product specific waiver for canakinumab (Ilaris) (EMEA-000060-PIP09-20) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council The European Medicines Agency, for all subsets of the paediatric population and the mentioned condition(s) in accordance with Article 11(1)(b) of said Regulation, on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in adult populations.

4.1.4. General comments on compliance with GLP, GCP

In the pre-submission meeting, the MAH was specifically requested to describe measures taken to assure that the principles of GCP were adhered with in Study DDE03T. MOs and several OC's proposed reflect potentially major issues in study conduct, documentation and reporting, and the quality basis of the main study therefore cannot be duly confirmed from a GCP perspective. The documentation provided by the MAH is not considered overall fit for regulatory purposes. The MAH is requested to provide a complete ICH E3-compliant CSR, including appropriate documentation of statistical methods and supported by sufficient tabular summaries, to enable an appropriate clinical and statistical assessment of the study (it is acknowledging that the SAP may need to be prepared post hoc).

The irregularities in the randomisation process raise substantial concerns regarding the validity of the statistical analyses as presented in documentation submitted by the MAH. The overall GCP compliance of the study is seen questionable and the responses provided by the MAH do not overall mitigate the previously stated concerns. Due to the substantial deficiencies, it is questioned whether the ILESCH study, as presented in the submitted documentation, could serve as an adequate basis to support a positive opinion for the variation application.

4.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

4.3. Clinical aspects

4.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP and the Declaration of Helsinki as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of key studies and their status

Source of data	Details
Study DDE03T (ILESCH)	Phase II, multicenter, randomized, double-blind, placebo-controlled, IIT of canakinumab in SchS patients [Study DDE03T].
Literature review	Comprehensive review of the scientific literature of canakinumab and other IL-1 inhibitors (anakinra and rilonacept) used in SchS, with a cut-off date of 31-Jan-2021 [ACZ885 SchS Literature Review 2021]
Supportive safety data	In CAPS: Study A2102, D2201, D2304, D2306 and D2308; in AOSD: Study GDE01T; in post-MI patients: Study M2301.

4.3.2. Pharmacokinetics

No PK data were collected in Study DDE03T.

4.3.3. Pharmacodynamics

4.3.4. PK/PD modelling

The pooled dataset used in the population PK simulation included a total of 31 studies in CAPS, healthy volunteers as well as various other disease populations (e.g., SJIA, gouty arthritis, rheumatoid arthritis, and psoriasis) including their extensions with more than 1700 patients worldwide (non-Japanese and Japanese) treated with canakinumab.

The pharmacokinetics of canakinumab in various disease populations (e.g. asthma, CAPS, SJIA, gouty arthritis, rheumatoid arthritis, and psoriasis) are comparable to those in healthy individuals (see also Figure 1 below). No sex- or age-related pharmacokinetic differences were observed after correction for body weight. But age was identified as statistical significant covariate on absorption rate and disease population on CL (see pop PK mode Table 1).

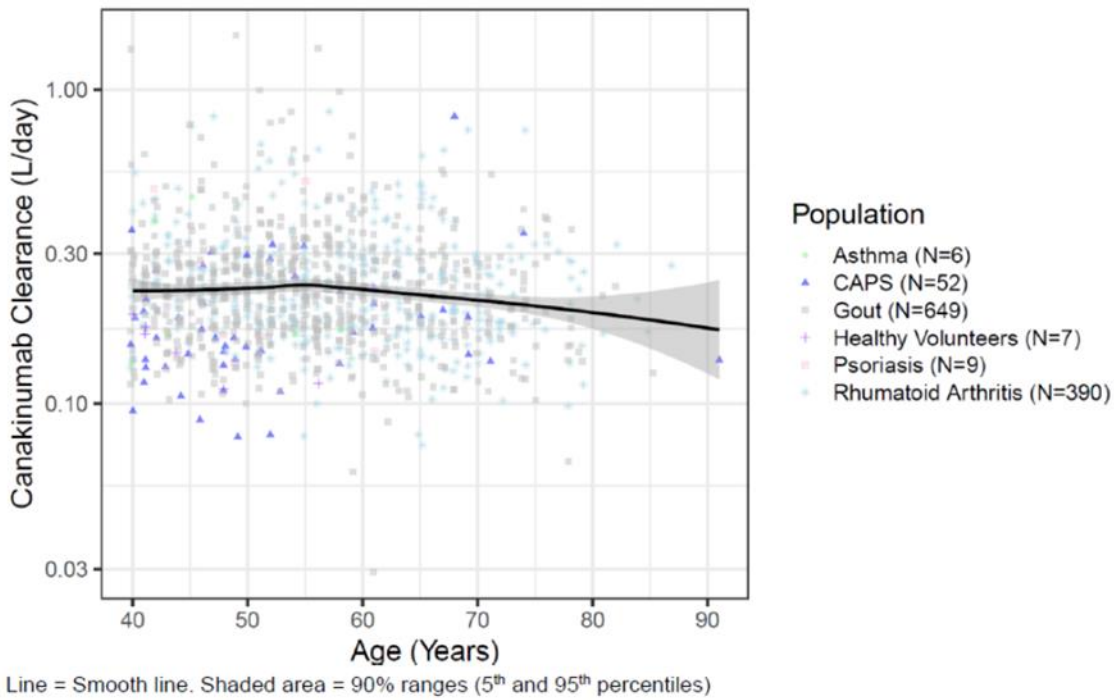


Figure 1 Individual predicted clearance (L/day) of canakinumab versus age in various diseases

Earlier exploratory analysis of PK data from a small open label study in patients with SchS using an every 4-week dosing regimen had concluded consistency of PK in SchS patients with CAPS and gouty arthritis patients (Bhansali et al 2013), supporting the PK modelling approach. Of note, the apparent clearance (CL/F) estimated in the earlier exploratory analysis of 0.279 L/day is close to the apparent clearance used in our simulations, that can be derived from the clearance for a median body weight and the bioavailability (F) (Table 1 below).

Population PK model

The population PK model was used for simulation. Between subjects variability was included.

Correlations between patient-specific random effects, between the clearance and the central volume and between the peripheral volume and the inter-compartmental flow were included.

The model also included an additive residual error term and covariate adjustments.

Population

A subset of the pooled dataset was used for simulation purpose. Demographic data (age, weight) of 1113 (non-Japanese) patients above or equal 40 years of age were selected from the pooled dataset. The

median weight was 85.5 kg and their median age was 55 years (from 40 to 91).

Population PK simulation

The model previously developed was used to generate individual predictions of canakinumab exposure over 1 year with the dosing scheme of 150 mg Q8W. Since the pharmacokinetics of canakinumab is comparable among diseases as stated before and because of the similarities between CAPS and SchS, the patients were simulated.

Table 1 Parameter estimates of population PK-binding model

Parameter [units]	Population mean θ ± SE (%RSE) [95% Confidence Interval]	Inter-individual variance ω^2 ± SE (%RSE) [95% Confidence Interval]	Coefficient of Variation (CV)	Shrinkage [1]
Canakinumab parameters				
ACZ Clearance – 70 kg (CL, L/day at 43 g/L albumin)	0.188 ± 0.0116 (6.17%) [0.1764 – 0.2107]	0.129 ± 0.00876 (6.79%) [0.1202 – 0.1462]	35.92%	7.01%
ACZ Clearance – 33 kg (CL, L/day at 43 g/L albumin)	0.102 ± 0.00577 (5.66%) [0.0962 – 0.113]			
Central distribution volume – 70 kg (Vc, L) Non-Japanese	3.44 ± 0.191 (5.55%) [3.249 – 3.814]	0.24 ± 0.03 (12.5%) [0.21 – 0.298]	48.99%	19.99%
Central distribution volume – 33 kg (Vc, L) Non-Japanese	1.55 ± 0.0967 (6.24%) [1.453 – 1.740]			
Peripheral distribution volume – 70 kg (V_P, L) Non-Japanese	2.88 ± 0.126 (4.38%) [2.754 – 3.127]	0.0471 ± 0.0109 (23.1%) [0.0362 – 0.0685]	21.7%	53.66%
Peripheral distribution volume – 33 kg (V_P, L) Non-Japanese	1.71 ± 0.0915 (5.35%) [1.619 – 1.889]			

Inter-compartmental permeability flow (L/d)	0.658 ± 0.054 (8.21%) [0.604 – 0.7638]	0.0564 ± 0.0296 (52.5%) [0.0268 – 0.1144]	8.48%	82.78%
Absorption rate constant (ka, 1/d)	0.277 (0.265-0.301)	0.189 ± 0.036 (19.0%) [0.153 – 0.260]	43.47%	47.04%
Bioavailability (F1, %)	70.95 (67.28-77.38)			
Covariates				
SJIA Japanese on CL^2	-22.2%± 5.5 (24.77%) [-14.95 – 0.0003]			
Healthy Volunteers, Japanese on CL^2	-9.89%± 5.06 (5.12%) [-14.95 – 0.0003]			
Healthy Volunteers, Non-Japanese on CL^2	-19.8%± 4.8 (24.24%) [-24.6 – -10.4]			
CAPS Non-Japanese on CL^2	-5.8% ± 4.32 (74.48%) [-1.38 – 19.1]			
CAPS Japanese on CL^2	10% ± 8.17 (81.7%) [1.83 – 26.0]			
Psoriasis on CL^2	5.54% ± 6.92 (125%) [-1.38 – 19.1]			
Gouty Arthritis on CL^2	3.63% ± 5.08 (140%) [-1.45 – 13.6]			
Asthma on CL^2	-5.57%± 6.79 (122%) [-12.36 – 7.73]			
Rheumatoid Arthritis on CL^2	14.9% ± 5.36 (3.60%) [9.54 – 25.4]			
Japanese on Vc and Vp^3	-9.64% ± 2.72 (28.2%) [-12.36 – -4.31]			
Weight on CL	0.812 ± 0.0299 (3.68%) [0.7821 – 0.8706]			
Albumin on CL	-1.19 ± 0.084 (7.06%) [-1.274 - -1.02536]			
Weight on Vc	1.07 ± 0.0472 (4.41%) [1.023 – 1.163]			
Weight on V_P	0.693 ± 0.0345 (4.98%) [0.659 – 0.761]			
Age on k_A	-0.371 ± 0.0413 (11.1%) [-0.412 - -0.290]			
Covariances in OMEGA matrix				
CL:Vc		0.14 ± 0.0147 (10.5%) [0.125 – 0.169]		
V_P:Q		0.00437 ± 0.07 (16.0%) [-0.0656 – 0.1416]		
Residual variances				
Canakinumab (µg/mL)	0.0713 ± 0.0046 (6.45%) [0.0667 – 0.080]		26.7%	

[1]Inter-subject variance shrinkage for each eta is evaluated as: 100%*[1-SD(eta(i))/sqrt(omega(i,i))], where i is a subject [2]Disease as SJIA typical value x(1+θ) [3]Displayed as non-Japanese value x(1+θ)

The exponents for the power model of weight, age and albumin were centered respectively on 70kg/33kg, 34 years and 43g/L.

The procedure was repeated in order to predict the pharmacokinetics of canakinumab in patients using the demographic data of the 1113 selected patients.

The analysis was performed. Data preparation and graphical exploration were performed.

Results

The median time course (with 90% prediction intervals) of predicted canakinumab concentrations for patients with SchS is shown in Figure 2 below. Note that from the population PK model, the clearance used for simulation 0.21 L/day reflected the median body weight 85.5 kg of the simulated typical patient with SchS. Some accumulation is visible until month 4 with little further increase in concentrations afterwards (pharmacokinetics at steady state).

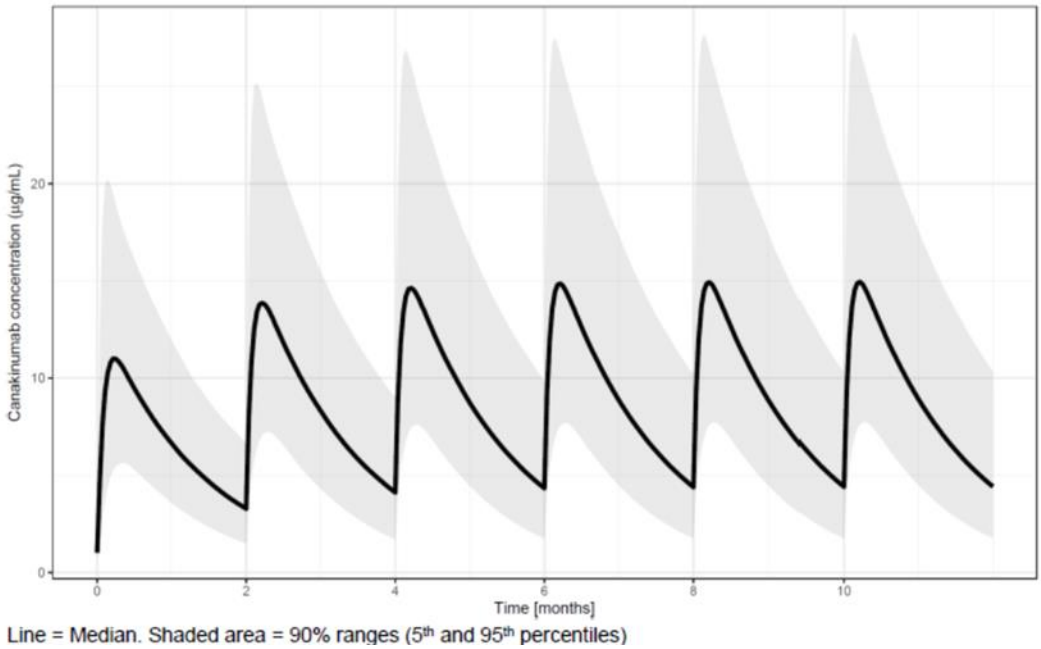


Figure 2 Time course of predicted canakinumab concentrations for patients with Schnitzler syndrome (150 mg every 8 weeks)

Figure 3 shows canakinumab exposure in patients with SchS using different individual predicted metrics of exposure at steady state (CMINss, CMAXss, AUCss).

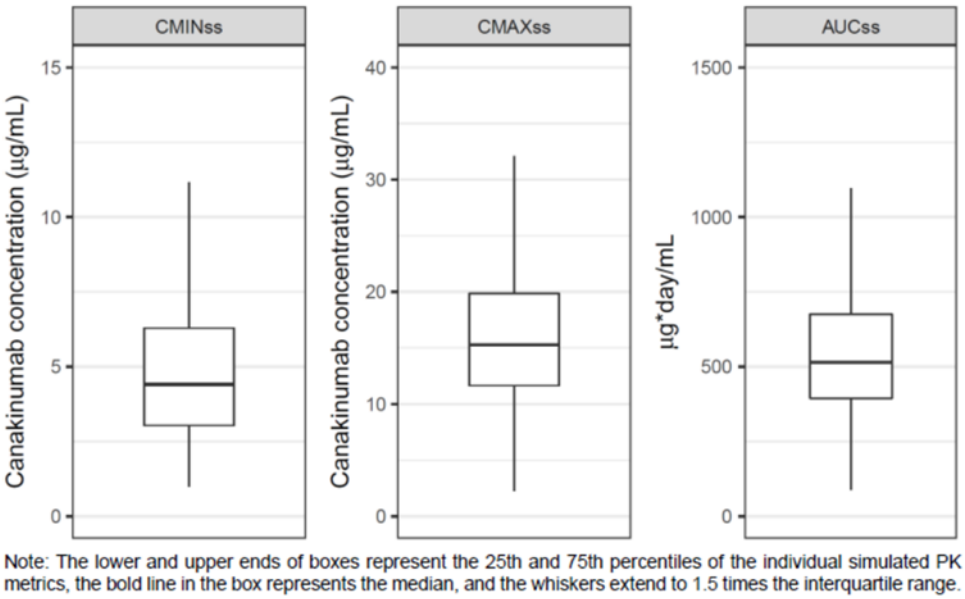


Figure 3 Predicted steady-state metrics of canakinumab exposure at steady-state for patients with Schnitzler syndrome

4.3.5. Discussion on clinical pharmacology

No PK data were collected in Study DDE03T. The canakinumab PK shows similarity over a range of diseases characterized by chronic inflammation including SJIA, CAPS, gouty arthritis, rheumatoid arthritis and psoriasis, while covariate effects have been identified on CL. Clinical similarities of the Schnitzler syndrome with other genetically determined auto-inflammatory syndromes like CAPS. The

PK of patients with SchS was predicted from patients with CAPS for a dose of 150 mg Q8W and a patient population with an age range that is typical for patients with SchS.

An earlier exploratory analysis of PK data from a small open label study in patients with SchS using a Q4W dosing regimen had concluded consistency of PK in SchS patients with CAPS and gouty arthritis patients. A subset of the pooled dataset was used for simulation purpose. Demographic data (age, weight) of 1113 (non-Japanese) patients with a body weight between 40 and 155 kg (median 85.5 kg) and an age of 40 to 91 years (median 55 years) were selected from the pooled dataset.

Simulations were performed by fixing model parameters at their final estimated values while setting the disease effect to CAPS and updating post-hoc predictions without running the fitting algorithm (MAXEVAL=0 option in NONMEM). The procedure was repeated 10 times in order to predict the pharmacokinetics of canakinumab in more than 11000 patients using the demographic data of the 1113 selected patients.

For patients with SchS dosed at 150 mg canakinumab every 8 weeks, the median predicted CMINss, CMAXss concentration and AUCss of canakinumab at steady state are respectively 4.41 µg/mL (range [1.76-10.3]), 15.3 µg/mL (range [7.86-28.4]), and 515 µg*day/mL. If the dose is increased to 300 mg Q8W to achieve adequate symptom control, the exposure is expected to be approximately 2-fold higher.

4.3.6. Conclusions on clinical pharmacology

The PK of canakinumab has been characterized in several disease especially in those characterized by chronic inflammation. The PK of patients with SchS was predicted by the applicant from patients with CAPS for a dose of 150 mg Q8W. It is known that there are clinical similarities of the Schnitzler syndrome with other genetically determined auto-inflammatory syndromes like the cryopyrin-associated periodic syndromes (CAPS). Therefore, this approach is reasonable.

No PK data were collected in Study DDE03T. However, the PK and dose-exposure relationship for canakinumab administered s.c. were characterized across indications and no relevant impact of disease condition on PK was identified (Chakraborty et al 2012). Therefore, the systemic exposure to canakinumab is expected to reach similar exposure ranges patients with SchS compared to other indications (CAPS) for the suggested dosing regimen.

4.4. Clinical efficacy

4.4.1. Dose response study

Not applicable.

4.4.2. Main study

Due to the rarity of SchS worldwide, only one randomized, placebo-controlled trial in patients with Schnitzler Syndrome has been conducted by the applicant.

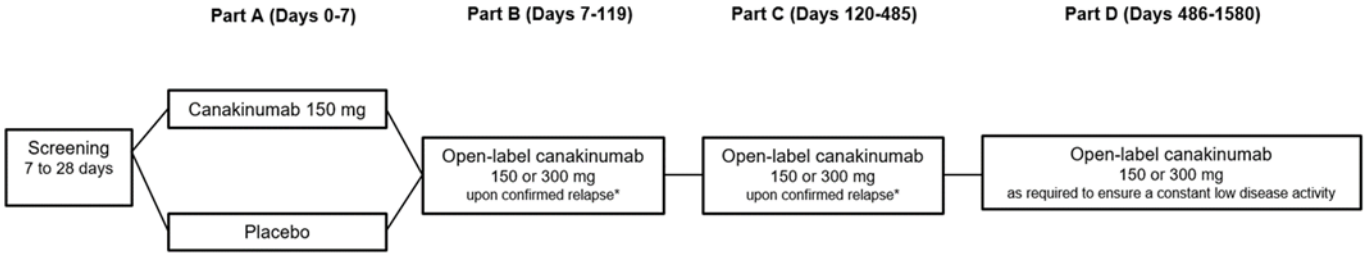
Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CACZ885DDE03T (ILESCH) **Countries**: Germany **Start**: 05-Jul-2011 **End**: 21-Dec-2017	**Design, purpose & population**: A multi-center, double-blind, placebo-controlled phase II study of the efficacy and safety of canakinumab in subjects with Schnitzler syndrome (ILESCH)	**Total**: Part A and Part B: 20 Part C and Part D: 17 Part A,B,C, D completed: 15 **Age**: 28-74 (60.5) years Groups: 2 Group 1: 20 Group 2: 17	**Form(s)**: canakinumab 150 mg or 300 mg, injection (s.c.) matching placebo 1 mL, injection (s.c.) **Duration**: Part A: Days 0-7 Part B: Days 7-119 Part C: Days 120-485 Part D: Days 486-1580 **Doses:** canakinumab 150mg or 300mg matching placebo	**Study Status**: complete **Report no.1** [CACZ885DDE03T int] interim, complete Parts A and B **Report date:** 13-Nov-2013 **Report no. 2** [CACZ885DDE03T] full, final **Report date**: 20-Dec-2018

Title of Study

Study DDE03T (ILESCH)

A multi-centre, double-blind, placebo-controlled phase II study of the efficacy and safety of canakinumab in patients with Schnitzler syndrome.

Methods



* Minimum interval between canakinumab doses is 2 weeks. Relapse within 2 weeks of a canakinumab dose may be treated with systemic corticosteroids of individualized dosage.
Note: Placebo patients received their first dose of canakinumab 150 mg on Day 7. Complete responders continued to receive canakinumab 150 mg upon subsequent relapses, partial responders received another 150 mg dose at Day 14 and 300 mg upon subsequent relapses.

Study DDE03T was a Phase II, multicentre, randomized, double-blind, placebo-controlled, investigator initiated trial (IIT) that evaluated safety and efficacy of canakinumab in SchS patients. The study was conducted in 4 centres in Germany.

20 patients were eligible and randomized into the study. Seven patients were randomized to the canakinumab-treated group and 13 to the placebo group. After a 7-day double-blind part of the study (Part A), all patients switched to a >4-year open-label long term extension canakinumab treatment period consisting of multiple study parts (Parts B, C and D).

Part A was a 7-day double-blind, placebo-controlled study of a single SC dose of canakinumab 150 mg. Patients were randomly assigned to receive canakinumab 150 mg or placebo at Day 0 (7 patients were randomized to the canakinumab-treated group and 13 to the placebo group). The difference in group

sizes was due to inadvertent imbalance in study drug distribution between study centres. Following treatment response evaluation at Day 7, patients were unblinded and moved to the open-label phase.

Part B was a 16-week open-label follow-up phase to establish the optimal dose of canakinumab (150 mg or 300 mg) and to further assess AEs. The canakinumab doses were based on individual clinical and laboratory responses at the end of Part A.

- Based on Physician's Global Assessment (PGA) patients with a complete clinical response to canakinumab 150 mg and normalized CRP levels at the end of Part A continued with canakinumab 150 mg injections upon confirmed relapse of symptoms (defined as a ≥50% increase in the PGA total score as compared to the PGA total score 7 to 14 days after canakinumab administration).
- Partial responders to canakinumab 150 mg with or without CRP above the upper limit of normal (>0.5 mg/dL) were given canakinumab 150 mg on Day 7 and were given canakinumab 300 mg upon relapse (worsening of symptoms).
- Placebo patients without clinical response received the first canakinumab 150 mg dose on Day 7. Complete responders continued to receive canakinumab 150 mg upon subsequent relapses, partial responders received another 150 mg dose at Day 14 and 300 mg upon subsequent relapses.

Parts C and D comprised a 4-year open-label extension to evaluate long-term efficacy, quality of life, and safety. Duration of Part C was 1 year and of Part D 3 years. All patients who successfully completed the initial 4 months of the study (Parts A and B) were eligible to enter open-label extension phase.

- During Part C, patients were taking either canakinumab 150 mg or 300 mg based on previous individual responses in Parts A and B. Canakinumab was administered upon confirmed relapse of symptoms.
- For the following 3 years (Part D), canakinumab was given as needed based on previous responses in Part C (individual mean dosing intervals) to ensure a constant low disease activity and low inflammatory.

Study participants

Patients with symptomatic SchS based on diagnostic criteria by Lipsker and colleagues (Lipsker et al 2001) were included. Eligible were male or female patients of 18 years or older with symptomatic SchS (PGA total score of 8 or more [range, 0-20] and CRP level above the ULN at visit 2 [Day 0]). Females of childbearing potential had to have a negative pregnancy test and had to use highly effective contraception. Excluded were patients with active and chronic infections (e.g. tuberculosis, HIV, HBV, HCV), current or ongoing treatment with IL-1 blockers (or recent treatment within 48 prior to Day 0) as well as current or ongoing treatment with other biologics or immunosuppressive drugs including high doses of systemic steroids. Further excluded were patients with significant medical condition rendering the patient immunocompromised or not suitable for a clinical trial and with presence of malignancies within the last 5 years.

20 patients were enrolled. 45% (n=9) were female and 55% (n=11) were male patients. The median age was 62 years and 64 years in the canakinumab and placebo groups, respectively. The median duration of disease was 5.5 and 6.3 years, respectively, ranging from 1.5 years to 22 years. The majority of patients presented with symptoms of fatigue, myalgia and arthralgia/bone pain at baseline, and all patients had urticarial rash and monoclonal paraproteins (mainly IgM) as major diagnostic criteria prior to enrolment.

Eight of 20 patients (3 from the canakinumab group and 5 from the placebo group) had previously received anakinra treatment and had stopped treatment at least 3 days (>5 half-lives) before canakinumab treatment initiation at Day 0.

CHMP comment

The eligibility criteria are acceptable and define an adequate patient population with Schnitzler Syndrome. Only 20 patients were enrolled due to the rarity of the disease. Additionally the randomization was unbalanced with 7 patients in the canakinumab group and 13 patients in the placebo group. The MAH explains that this difference between the groups appeared due to inadvertent imbalance in study drug distribution between study centres. The clarification presented by the MAH with the D121 Responses is considered insufficient, so the issue remains. It is noteworthy that the imbalance seems to be mainly based on the distribution of the kits to the 3 additional sites. Only one patient in all of these three sites received canakinumab.

Treatments

The initial canakinumab dose of 150 mg was selected for Part A of Study DDE03T based on the consideration of the clinical and pathophysiologic similarity of CAPS and SchS. The approved canakinumab dose in CAPS is 150 mg, administered s.c. Q8W.

Part B was a 16-week open-label follow-up phase to optimise the canakinumab dose. Based on Physician's Global Assessment (PGA) patients with a complete clinical response received 150 mg upon confirmed relapse. Partial responders to canakinumab 150 mg with or without CRP above the upper limit of normal (>0.5 mg/dL) received canakinumab 150 mg on Day 7 and were given canakinumab 300 mg upon relapse. Patients from the Placebo group who had no clinical response received the first canakinumab 150 mg dose on Day 7. Complete responders continued to receive canakinumab 150 mg upon subsequent relapses, partial responders received another 150 mg dose at Day 14 and 300 mg upon subsequent relapses.

In Part C of the study, patients were taking either canakinumab 150 mg or 300 mg based on previous individual responses in Parts A and B. Canakinumab was administered upon confirmed relapse of symptoms. The median dosing interval was 62-63 days (62 days for patients receiving canakinumab 150 mg, n=8 and 63 days for patients receiving canakinumab 300 mg, n=9), which could be comparable to the 8-week dosing regimen used for CAPS. However, dosing intervals over the whole study ranged from

28 days to at least 1 year (3 patients who received canakinumab 150 mg were symptom free for at least 12 months), with the time to relapse inversely correlated with disease activity. Individual dosing regimens of the 17 patients included in the open-label extension phase are presented below.

In Part D canakinumab was given as needed based on previous responses in Part C (individual mean dosing intervals). Relapse of symptoms was not required for canakinumab dosing during Part D. One patient increased their canakinumab dose from 150 mg to 300 mg at the end of the second year of the study (Part D) due to increased musculoskeletal complaints.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including a figures illustrating the dosing schedule, please refer to Krause et al 2017.

CHMP comment

The double-blind part A of Study DDE03T lasted only 7 days and in the following open-label parts B and C canakinumab was administered upon confirmed relapse of symptoms. In part D the individual dosing regimen established in part C was continued. The proposed Q8W dosing regimen has not been tested in study DDE03T. The sponsor claims that the median canakinumab dosing intervals during the open-label extension phase of Study DDE03T were with 62 days (150 mg) and 63 days (300 mg) comparable to the 8-week dosing regimen recommended for SchS. However, the data show that the dosing intervals over the whole study ranged from 28 days to at least 1 year. With the Responses to Request for Supplementary Information, the MAH revised the wording of the indication to allow a more flexible dosing with regards to shorter dosing intervals of a minimum of every 4 weeks. This is expected to lead to similar efficacy results as several patients had a shorter dosing interval. However, it is not clear whether the safety results would be similar, especially for patients without a relapse and canakinumab administration in 12 month. In Part B 20% of patients were without a relapse for 16 weeks and in Part C 17.6% of patients were without a relapse for 12 month. Furthermore, due to the case of fatal sepsis a statement should be implemented to stop treatment if insufficient efficacy is seen. (MO)

Objectives

Primary objective:

- To assess the effect of canakinumab on the clinical signs and symptoms of SchS

Secondary objectives:

- To assess the safety of canakinumab in subjects with SchS
- To assess the change in biomarkers of inflammation (C-reactive protein, serum amyloid A, erythrocyte sedimentation rate) during the treatment period with canakinumab
- To assess changes in patients' quality of life during the treatment period with canakinumab

Exploratory objective:

- To assess the effect of canakinumab on mast cell activation in the skin of SchS patients

Outcomes/endpoints

- The **primary endpoint** of the study was the proportion of patients with complete clinical response based on PGA measurements at Day 7 of Part A. For the PGA, five key symptoms (urticarial rash, fatigue, fever/chills, myalgia, arthralgia/bone pain) were measured on a 5-point scale to assess the overall auto-inflammatory disease activity.

  A **complete clinical response** was defined as no or minimal disease activity (i.e., a PGA total score of 5 or less and no greater than 1 in any of the 5 key symptoms).

  A **partial clinical response** was defined as mild to moderate disease activity with a PGA total score of more than 5 and a PGA reduction of 30% or more as compared with baseline. No clinical response was defined as high disease activity with PGA total scores that were increased, stable, or showed less than 30% reduction compared to baseline

- **Key secondary efficacy endpoints** included:

- PGA of disease activity
- Schnitzler activity score (documented using a patient-based Daily Health Assessment Form that was previously validated for CAPS (Krause et al 2012)
- Inflammatory markers (CRP, SAA and ESR)
- Although ESR was a secondary endpoint, results for this parameter were not reported (OC) as assessment of CRP and SAA was of greater relevance for patients with SchS
- Quality of life assessment: Dermatology Life Quality Index (DLQI), 36-item short form health survey (SF-36).

CHMP comment

The objectives and endpoints are adequate.

Sample size

As Schnitzler Syndrome is a rare disease, the sample size of 20 patients was not based on formal considerations, but it was based on the investigator's experience with minor pilot studies about the treatment of urticaria. The Applicant presents some scenarios describing combinations of values of expected placebo and treatment effects sufficient to reach significant differences with 0.05 alpha level and 80% power.

CHMP comment

In principle, the choice is acceptable.

However, the motivation ("investigator's experience") is weak and should have been further justified (e.g. reference to previous studies, feasibility considerations).

In the Responses to Request for Supplementary Information, the MAH repeated the justifications presented in the CSR and did not add new substantial information. Additional literature to support the sample size was provided as part of the literature review, but specific sources were not referenced in the answer, which is unsatisfying. The MAH reported the power calculation performed in the study protocol assuming a 1:1 randomisation, but did not discuss the impact of the actual 2:1 group distribution on the power.

Furthermore, the MAH remarks that this was a "pilot study", but now interprets the results in the context of a confirmatory trial to support a Type II Variation. While it is acknowledged that SchS is a rare indication, the methodological flaws of the trial cannot be ignored. The results from this pilot study should not be interpreted as confirmatory evidence, but they could and should be used to inform a subsequent trial.

Randomisation

At page 25 of the Clinical Study Report, the Applicant states that randomization was carried out by a pharmacy. In the study flowchart (page 31 of the Clinical Study Report (CSR)), the Applicant states that 7 study participants were allocated to Canakinumab and 13 to placebo. Patients were randomized to receive either canakinumab 150 mg or placebo 150 mg s.c. injections at day 0. No further information about the randomization procedure or its implementation is reported in the CSR or in the submitted protocols.

CHMP comment

According to the Guideline on clinical trials in small populations (CHMP/EWP/83561/2005) "controlled studies with low statistical power in case of an important treatment effect may be preferable to no controlled studies". Therefore, in principle, the effort to conduct a controlled, randomized trial is appreciated.

The study was planned with a 1:1 randomisation. A randomisation list of length 40 with randomisation blocks of size 10 was generated (the MAH provided the full randomisation list but not information on the algorithm used). However, due to an imbalance in the study kit distribution, the actual randomisation of the participant was 7 (canakinumab): 13 (placebo). The MAH did not provide further details regarding the actual distribution of the kits.

The submitted information regarding randomization remains insufficient. .Large imbalances in relevant covariates (see Baseline demographic, clinical and laboratory characteristics across the study groups), albeit in standard physiological ranges, raise questions about the validity of the randomization.

Additionally it was noticed that the MAH reports that 21 patients were screened into the study, 1 was a screen failure, and 20 were randomised. However, according to the randomisation list, numbers 1 to (at least) 27 were assigned (see e.g. response to OC4). It is not clear whether the remaining 6 randomisation numbers were assigned to non-eligible patients that were not disclosed in the CSR, or whether they were not assigned, and whether this issue is related to the study kits distribution.

Overall, the issues hint towards a violation of GCP procedures, and additional justification by the MAH is requested. The MAH is asked to explain how the kits were actually distributed to the study sites, especially considering that patient recruitment was conducted mainly at the site, and to justify the seemingly missing randomisation numbers. (MO)

Blinding (masking)

The applicant states that canakinumab and placebo were practically identical in aspect and the primary packaging was identical, thus, the type of drug could only be identified by means of the randomisation list and the emergency envelopes, and that the code was never broken during the open-label study despite the possibility to break the code for an individual patient in case of serious or unexpected adverse events.

CHMP comment

The submitted information suggests that injectors, patients and evaluating physicians were blind to the allocated treatment, which is endorsed. The Applicant states that "the code was never broken during the open-label study", which does not match the study design (unblinding at the end of part A). It is expected that this was a typo and that the Applicant meant "the code was never broken during the blinded study". The MAH clarify the typo with the Responses to the Request for Supplementary Information.

Statistical methods

The Applicant presents the data analysis methodology after the presentation of the results (page 41ff of the Clinical Study Report (CSR)). The Applicant states that FAS, PPS and SAF populations were used for all statistical analysis. Briefly, the Applicant states to analyse the data in a descriptive way and mentions that paired t-tests and non-parametric tests (Mann-Whitney-U tests, Wilcoxon signed rank tests) were

planned to be used. Earlier in the CSR (page 16), the Applicant presents expectable scenarios for efficacy which were calculated based on exact Fisher test.

CHMP comment

In the response to the Request for Supplementary Information, the MAH clarified that FAS was used for the reports in the CSR and that Fisher's exact test with a 2-tailed significance level of 5% was used to analyse the primary endpoint.

Results

Participant flow

Twenty-one patients were screened, and 20 of them underwent randomization and received at least 1 dose of study drug between July 23, 2011, and August 17, 2012 (Krause et al 2017).
Of these, 7 were assigned to the canakinumab-treated group and 13 were assigned to the placebo group. This difference in group sizes was caused by an inadvertent imbalance in study drug distribution between the study centers due to an error in the ratio of placebo versus canakinumab in a subset of study medication that one of the study centers was provided with, which resulted in higher than intended numbers of patients treated with placebo during the double-blind, controlled phase of the study. All randomized patients received at least 1 treatment, completed the double-blind and open-label phase of the study, and were included in the primary end-point analysis and safety analysis (Krause et al 2017).

For complete details of figures and tables, please refer to Krause 2020.

CHMP comment

20 patients were enrolled. 15 patients completed the long-term extension phase. It is noteworthy that due to the irregularities in the randomisation and IMP allocation process, there is an extreme imbalance between treatment groups at the participating centre level: except for 1 patient at site X, all patients receiving active drug were enrolled at site X. Consequently, whereas at site X there are 6 patients on canakinumab and 7 patients on placebo, there is only 1 patient on canakinumab and 6 patients on placebo across all the other participating sites.

Recruitment

First patient screened: 05.07.2011

First patient randomized: 23.07.2011

Last patient out: 21.12.2017

Conduct of the study

The protocol amendment for the open-label extension parts of the study (Parts C and D) was approved after some of the first patients had completed Parts A and B. For these individual patients, there may

have been a delay between the end of Part B and the start of Part C. During this delay, patients received individual anti-inflammatory treatment, if needed.

For the following patient a protocol deviation was recorded:

Patient X: The patient was categorized as complete responder although CRP levels were not normalized on day 7. Subsequently, he was treated with canakinumab 150mg in the open-label phase instead of 300mg upon relapse of symptoms.

CHMP comment

The MAH responded that the PI provided a probable rationale. The patient X had a good clinical response and was treated as complete responder. The investigator accidentally didn´t acknowledged the non-normalized CRP levels during Part B even though CRP levels and the PGA Score were clearly described in the protocol as the main parameter to classify responders.

The probable justification presented by the MAH is vague and not satisfying. It is one more issue that casts the GCP compliance in doubt.

Baseline data

45% (n=9) were female and 55% (n=11) were male patients. Different values for the median age are presented in the reports of the dossier and should be clarified by the applicant (OC). The median duration of disease was 5.5 and 6.3 years, respectively, ranging from 1.5 years to 22 years. The majority of patients presented with symptoms of fatigue, myalgia and arthralgia/bone pain at baseline, and all patients had urticarial rash and monoclonal paraproteins (mainly IgM) as major diagnostic criteria prior to enrolment.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause 2017.

At baseline, markers of systemic inflammation (CRP and SAA) were elevated in both groups, although higher in the canakinumab-treated group. Eight of the 20 patients (canakinumab n=3, placebo n=5) had previously responded to the IL-1 inhibitor, anakinra, and stopped treatment at least 3 days before canakinumab or placebo treatment initiation at Day 0.

Numbers analysed

20 patients were screened and found to be eligible. All patients received study medication. All patients completed all visits within the 4-month study period. All patients were included in the analysis (n=20).

N (total) = 20 patients with SchS (included in part A and B)
N=17 patients entered open-label extension (part C and D)
N=15 patients completed whole study period (4 years)

Outcomes and estimation

Currently, the assessment of efficacy from this study is compromised by the lack of appropriate documentation according to ICH standards, including statistical analyses and results (MO), and the unclear circumstances related to randomisation (MO and OCs). Therefore, at this stage, the assessment is only preliminary, pending answers to the MOs. In addition, the appropriateness of the used Physician's Global Assessment (PGA) for this indication has not been adequately justified (OC).

Complete clinical response based on PGA of disease activity at Day 7

On day 7, the rate of complete clinical response (primary end point), that is, no or minimal disease activity, was significantly higher in the canakinumab-treated group (n=5 of 7 patients) than in the placebo group (n=0 of 13 patients) (P=0.001). Baseline disease activity, as determined by total PGA, was comparable in the canakinumab-treated group (median, 14; range, 8-20) and in the placebo group (median, 15; range, 8-20). At the end of the double-blind treatment phase (day 7), disease activity was significantly reduced from baseline (day 0) in the canakinumab-treated group (P=0.018), but not in the placebo group. The difference in median changes in PGA total scores (canakinumab -11 vs placebo 0) was significant between treatment groups (P < 0.0001) (Krause et al 2017).

The changes in CRP, SAA, and IL-1Ra levels were significantly different between treatment groups (Krause et al 2017). There were no significant changes in quality-of-life impairment in placebo treated patients (DLQI, P=0.270; SF-36 physical component, P=0.787). Between treatment groups, the changes for both, the DLQI sum scores and the physical component summary of the SF-36, were highly significantly different (P <0.0001) (Krause et al 2017).
For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables referenced above, please refer to Krause et al 2017.

- **Part A - 7-day double-blind, placebo-controlled study of a single SC dose of canakinumab 150 mg**

- **Primary endpoint**

  Complete clinical response based on PGA of disease activity at Day 7

  The study met its primary endpoint. The results show a higher proportion of patients with complete clinical response (no or minimal disease activity) in the canakinumab-treated group (n=5/7) compared to the placebo group (n=0/13) at Day 7 (p=0.001).

- **Secondary endpoints**

  PGA of disease activity

  At Day 7, a decrease in disease activity (PGA) was observed from baseline in the canakinumab-treated group (p=0.018). The difference in median changes in PGA total scores was -11 in canakinumab group vs. 0 in the placebo group with p<0.0001.

- **Part B – 16-week open-label phase (Days 7-119)**

All patients from the canakinumab-treated group (n=7) and the placebo group (n=13) moved from Part A to Part B due to the combined evaluation of clinical and laboratory responses. All 7 patients from the canakinumab-treated group in Part A continued with canakinumab and the 13 patients from the placebo group underwent treatment initiation with canakinumab.

Eight patients with complete clinical response and normalized CRP levels 7 days after canakinumab treatment initiation in Part B continued with canakinumab 150 mg doses. Twelve patients received canakinumab 300 mg doses because of slightly elevated inflammatory markers and/or remaining mild to moderate disease activity after canakinumab 150 mg initiation. All patients who switched to

canakinumab therapy from placebo showed clinical improvement, as indicated by reductions in PGA total scores, and the clinical improvement in patients who continued with canakinumab treatment from Part A was maintained.

Fifteen of 20 patients who had received either canakinumab or placebo in Part A were complete clinical responders and the remaining 5 were partial responders 7 to 14 days after canakinumab initiation in Part B.

At the end of the 16-week open-label phase, the positive effects of canakinumab on the clinical signs and symptoms of SchS were maintained, with PGA total scores reduced compared with baseline (median PGA total scores, 14.5 at Day 0 (at the start of Part A) vs. 3.5 at the end of Part B, $p<0.0001$).

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2017.

Relapse of clinical symptoms was reported in 14 patients, who subsequently received 1 to 3 additional canakinumab injections within this 16-week period.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2017.

- **Parts C and D – 4-year open-label extension phase (Days 120-485 and Days 486-1580)**

Secondary endpoints after 57-month (4-year) open-label extension phase (Parts C, D)	Canakinumab (N=17)*
PGA total score, median score and difference from baseline (baseline score: 14.5)	4 (0-5); p≤0.001
CRP, median difference from baseline	p≤0.001
SAA, median difference from baseline	p≤0.001
DLQI sum scores, median difference from baseline	p≤0.01
SF-36 physical component summary scores, median difference from baseline	p≤0.05
SF-36 mental component summary scores, median difference from baseline	p>0.05

*17 patients entered Part C and 16 patients entered Part D, while 15 patients completed the study period. Only the analysis of the primary endpoint is strictly confirmative and considered confirmatory; descriptive p-values for other analyses were not adjusted for multiplicity and cannot be assessed for statistical significance. Descriptive p-values are shown as a range for the different time points across the study compared to baseline.

17 patients entered the long-term, open-label extension phase. In Part C (1 year), patients continued the canakinumab dose (150 mg or 300 mg) based on previous individual responses in Parts A and B. During Part C, canakinumab was taken upon confirmed relapse (defined as at least a 50% increase in the PGA total score as compared with the PGA total score 7 to 14 days after initiation of canakinumab administration).

PGA total scores decreased from baseline (Day 0 at the start of Part A) and remained low throughout the study, up to 57 months.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2020.

Long-term canakinumab treatment provided continuous efficacy throughout the study with most patients experiencing no/minimal/mild disease activity. The results show lower PGA scores at all visits

from 6 months to 57 months compared to baseline ($p<0.01$). The median PGA total score was 14.5 at baseline. The score decreased to 9 at Month 6 ($p=0.0014$) and to 4 at Month 57 ($p=0.0007$).

Of note, overall PGA total scores were higher at the start of Part C compared to at the end of Part B (9 at Month 6 vs. 3.5 at the end of Part B). This was due to the delay in entering Part C for some of the patients, which contributed to a higher overall disease activity.

After 6 months of treatment, improvements in specific SchS symptoms were observed, including urticarial rash, fatigue and arthralgia/bone pain. Improvements in fever and myalgia were observed by 36 months.

The number of complete clinical responders at 6, 12, 36 and 57 months was 2/17, 3/17, 5/15 and 6/15 patients, respectively.

No substantial loss of efficacy over time was experienced by any of the patients. In 1 patient, increased musculoskeletal complaints (as assessed by PGA subscores for myalgia and arthralgia/bone pain), led to canakinumab dose escalation from 150 mg to 300 mg at the end of the second study year (Part D). Relapse of symptoms was rare, occurring mainly after treatment interruption (mainly due to the delay between Parts B and C) or infection (predominantly respiratory tract infections).

The higher disease activity and inflammatory marker levels at Months 6 and 12 as compared to Months 36 and 57 are explained by the study design, which required relapse of clinical symptoms for canakinumab treatment during the first year (Part C). However, clinical efficacy was maintained across Parts C and D of the study.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2020.

Lower disease activity, as measured by decreased total and individual PGA scores, allowed for prolonged dosing intervals (measured by injection intervals in days).

Patient-Reported Outcomes

- **Schnitzler activity scores** decreased during the first 7 days after initial treatment in Part A -5.5 in the canakinumab group compared to -1.9 in patients receiving placebo. Disease activity scores were reduced by 20% within 24 hours of canakinumab treatment, with clinically meaningful differences between the two groups achieved by Day 3 of treatment ($p<0.05$).

  For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2017.

- **Inflammatory markers (CRP and SAA)**

  <u>Part A – Randomized, double-blind, placebo-controlled phase (Days 0-7)</u>

  In the canakinumab-treated group, median serum levels of CRP decreased from 9.3 mg/dL at baseline to 0.6 mg/dL at Day 7 ($p=0.031$). Median SAA levels also decreased from 428 mg/L to 13 mg/L ($p=0.031$). In contrast, median CRP and SAA levels increased in the placebo group (3.1 to 5.0 mg/d/L, $p=0.685$ and 160 mg/L to 211 mg/L, $p=0.733$, respectively).

  <u>Part B – 16-week open-label phase (Days 7-119)</u>

At the end of the 16-week open-label phase, CRP and SAA levels were reduced compared to baseline.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2017.

Parts C and D – 4-year open-label extension phase (Days 120-485 and Days 486-1580)

Levels of both markers decreased following canakinumab administration and remained consistently low throughout the study, up to 57 months.

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2020.

Decreases and normalization in CRP levels were observed during the open-label extension phase of the study (descriptive p-value range across the different time points compared to baseline: p=0.04-0.0001). After 6 months, median CRP levels had decreased from 6.09 mg/dL at baseline to 1.02 mg/dL and remained within the reference level (≤0.5 mg/dL) at most subsequent visits. For 5 patients, CRP levels decreased but remained above the reference level. For 2 of these 5 patients, suboptimal clinical responses were observed and study treatment was discontinued due to serious AEs approximately at 10 months and 35 months after study treatment initiation. SAA levels also decreased during the study (15.8 mg/L at 6 months and 11.1 mg/L at 57 months; descriptive p-value range across the different time points compared to baseline: 0.03-0.0005).

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2020.

- **Quality of life assessment**

Part A

At baseline quality of life was considerably impaired in both treatment groups. Mean **DLQI** sum scores were reduced from moderate (8.2±2.4) to mild (2.8±1.7) impairment (p=0.003) within 7 days of canakinumab treatment.

Mean **SF-36** physical component summary scores improved from moderate impairment (32.8±4.6) at baseline to normal values (46.6±3.0) at Day 7 in patients treated with canakinumab. There was a numerical increase compared to placebo in the SF-36 mental component summary scores, but no clinically meaningful changes.

Part B

At the end of the 16-week open-label phase, quality of life scores based on the DLQI and the physical component of the SF-36 were improved compared to baseline.

For the **DLQI**, median scores decreased to 1 (range 0-25; p=0.006) following canakinumab treatment, which indicates that the patients' skin condition had no effect at all on the patients' life quality.

The **SF-36** physical component summary score increased to a mean (SD) value of 47.0 (42.7) (p=0.003). Despite numerical improvement, no changes were observed in the SF-36 mental component summary score, which increased from a mean (SD) value of 47.0 (31.6) to 50.7 (34.7) at the end of the open-label phase (p=0.058).

Part C

Quality of life improved in patients with SchS and improvement in the physical component summary of the SF-36 were maintained throughout the study, up to 57 months:

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2020.

Ancillary analyses

Not applicable.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2 Summary of Efficacy for trial CACZ885DDE03T

Title: A multi-center, double-blind, placebo-controlled phase II study of the efficacy and safety of canakinumab in subjects with Schnitzler syndrome		
Study identifier	Protocol number: CACZ885DDE03T Short title: ILESCH (**Il**aris **E**ffects in **Sch**nitzler Syndrome) EudraCT number: 2010-024156-28	
Design	This is a multi-center, randomized, double-blind, placebo-controlled, investigator-initiated trial of canakinumab in subjects with Schnitzler syndrome.	
	Duration of main phase:	- Screening period of up to 4 weeks - Part A (Days 0-7): Randomized, double-blind, placebo-controlled phase - Part B (Days 7-119): 16-week open-label phase
	Duration of Run-in phase:	None
	Duration of Extension phase:	Open-label extension phase, up to 4 years following Part B, which consisted of Part C (1 year) and Part D (3 years)

Hypothesis	This study is a pilot study intended to provide efficacy, safety and tolerability data in a small patient population of Schnitzler syndrome. With the small sample size and the unknown variability of the disease activity assessments in this population, statistical power considerations are unwarranted. Only the analysis of the primary endpoint was strictly confirmative for the hypothesis on superiority of canakinumab over placebo, and descriptive p-values for other analyses were not interpreted for statistical significance.		
Treatments groups (Part A)	Canakinumab (CANA)		Canakinumab 150 mg, single injection at Day 0 Days 0-7, 7 patients assigned, all completed
	Placebo (PBO)		Placebo, single injection at Day 0 Days 0-7, 13 patients assigned, all completed
Treatments groups (Part B)	Open-label		Canakinumab 150 mg or 300 mg upon confirmed relapse of symptoms based on the individual clinical and laboratory responses at the end of Part A. Days 7-119, 20 patients assigned, all completed
Treatments groups (Part C)	Open-label		Canakinumab 150 mg or 300 mg based on previous individual responses in Parts A and B. Days 120-485, 17 patients assigned, 16 completed
Treatments groups (Part D)	Open-label		Canakinumab 150 mg or 300 mg was given based on the individual mean dosing interval established in Part C. Days 486-1580, 16 patients assigned, 15 completed
Endpoints and definitions	Primary endpoint	Complete clinical response based on Physician's Global Assessment (PGA) measurements at Day 7	For the PGA, five key symptoms (urticarial rash, fatigue, fever/chills, myalgia, arthralgia/bone pain) were measured on a 5-point scale to assess the overall autoinflammatory disease activity: Absent – Minimal – Mild – Moderate – Severe The primary efficacy endpoint was the proportion of patients with complete clinical response based on PGA measurements at Day 7 (Part A). A complete response was defined as no or minimal disease activity (i.e., a PGA total score of 5 or less and no greater than 1 in any of the 5 key symptoms).

	Secondary endpoint	PGA of disease activity	For the PGA, five key symptoms (urticarial rash, fatigue, fever/chills, myalgia, arthralgia/bone pain) were measured on a 5-point scale to assess the overall autoinflammatory disease activity.
	Secondary endpoint	Schnitzler activity score	Schnitzler activity score (documented using a patient-based Daily Health Assessment Form that was previously validated for CAPS (Krause et al 2012)).
	Secondary endpoint	Inflammatory markers (CRP, SAA and ESR)	Although ESR was a secondary endpoint, results for this parameter were not reported as assessment of CRP and SAA was of greater relevance for patients with Schnitzler syndrome.
	Secondary endpoint	Quality of life assessment	- Dermatology Life Quality Index [DLQI; a skin disease-specific quality of life questionnaire] - 36-item short form health survey [SF-36; a generic health-related quality-of-life instrument])
Database lock	Date not available		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary endpoint of the study was the proportion of patients with complete clinical response based on PGA measurements at Day 7 of the double-blind phase of the study (Part A) in the canakinumab-treated group as compared to the placebo group. The primary endpoint used the Fisher exact test with alpha = 0.05 (two-sided).		
Descriptive statistics and estimate variability	Treatment group	Canakinumab	Placebo
	Number of subject	7	13
	Number of complete clinical responders based on PGA measurements	5	0
Effect estimate per comparison	Primary endpoint	Comparison group	Canakinumab *vs.* Placebo at Day 7
	Statistical methods	Fisher exact test with alpha = 0.05 (two-sided)	p=0.001
Analysis description	**Key Secondary analysis:** PGA of disease activity, median change (range), canakinumab vs placebo		

Analysis population and time point description	All patients, Day 7 (Part A)			
Descriptive statistics	Treatment group	Canakinumab	Placebo	
	Number of subjects	7	13	
	Median changes in PGA total scores	- 11 (-18 to -3)	0 (-8 to 5)	
	Descriptive p-value	p<0.0001		
Analysis description	**Key Secondary analysis:** PGA of disease activity, median change			
Analysis population and time point description	All patients			
Descriptive statistics	Treatment group	Canakinumab		
	Time point	Number of Subjects	Median PGA score	Descriptive p-value
	Day 0 (Part A)	20	14.5	NA
	End of Week 16 (Part B)	20	3.5	p<0.0001
Analysis description	**Key Secondary analysis:** Patient-reported disease activity, modified Schnitzler activity score			
Analysis population and time point description	All patients, Day 7 (Part A)			
Descriptive statistics	Treatment group	Canakinumab	Placebo	
	Number of subjects	7	13	
	Mean change from baseline	- 5.5	-1.9	
	Descriptive p-value	p<0.05		
Analysis description	**Key Secondary analysis:** Inflammatory markers (CRP and SAA)			
Analysis population and time point description	All patients, Day 7 (Part A)			

Descriptive statistics	Inflammatory Marker	Time point	Baseline	Day 7	Descriptive p-value
	CRP	Median serum level (CANA)	9.3 mg/dL	0.6 mg/dL	p=0.002
		Median serum level (PBO)	3.1 mg/dL	5.0 mg/dL	
	SAA	Median serum level (CANA)	428 mg/L	13 mg/L	p=0.032
		Median serum level (PBO)	160 mg/L	211 mg/L	
Analysis population and time point description	All patients, End of Part B				
Descriptive statistics	Inflammatory Marker	Time point	Baseline	End of Part B	Descriptive p-value
	CRP	Median serum level (CANA)	6.09 mg/dL	0.3 mg/dL	p<0.0001
	SAA	Median serum level (CANA)	180 mg/L	13.3 mg/L	p=0.001
Analysis description	**Key Secondary analysis:** Quality of life assessment				
Analysis population and time point description	All patients, Day 7 (Part A), Canakinumab patients only				
Descriptive statistics	Quality-of-life scores	Time point	Baseline	Day 7	Descriptive p-value
	DLQI sum score	Mean ± SEM	8.2±2.4	2.8±1.7	p=0.003
	SF-36 physical component summary score	Mean ± SEM	32.8±4.6	46.6±3.0	p=0.008
Notes	There was a numerical increase compared to placebo in the SF-36 mental component summary scores, but no clinically meaningful changes. There were no clinically meaningful changes in quality-of-life impairment in placebo-treated patients.				

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled efficacy analyses were submitted.

Clinical studies in special populations

Not applicable.

Supportive data

The applicant submitted a review of the scientific literature of canakinumab used in SchS.

The clinical similarities of SchS to other auto-inflammatory disorders like CAPS and AOSD has led to the use of agents targeting IL-1β as a potential therapeutic option.

These studies have demonstrated the effectiveness of anti-IL-1 treatment in controlling signs and symptoms of SchS, implicating IL-1β as a critical player in the pathophysiology of this disorder. However, anti-IL-1 therapy cannot cure SchS, therefore continuous treatment to control the signs and symptoms is required.

De Koning (2014) summarized the published case reports included in a SchS database up until August 2014, demonstrating the effects of 35 different treatment modalities that have been reported in SchS and concluded that IL-1 blocking therapies were the most effective ones.

An update and adaptation to this list of different treatment modalities indicates that many patients with SchS benefit from IL-1 blocking drugs, with the highest evidence of efficacy arising from case reports or case series assessing the use of the IL-1Ra anakinra, followed by the monoclonal IL-1β specific antibody canakinumab (de Koning and Krause 2019).

In several cases the efficacy of anakinra (a recombinant form of human IL-1Ra, which binds to IL-1R inhibiting IL-1α and IL-1β signalling and thereby blocking the pro-inflammatory effects of the cytokine IL-1) has been reported (de Koning et al 2006, Ryan et al 2008, Loock et al 2010, Vandenhende et al 2011, de Koning 2014, Bashir et al 2018, Goodman et al 2019).

These case reports indicate that most patients respond within days after treatment initiation with a complete or nearly complete and long-lasting remission of symptoms.

Fewer clinical data are available for rilonacept, an IL-1 soluble receptor fusion protein which blocks IL-1 signalling. A small open-label study with eight patients who received weekly rilonacept injections reported a rapid clinical response, with reduction of inflammatory markers in patients with SchS. Anakinra is administered by daily injections, while rilonacept is administered once weekly. Case reports and controlled trials on the successful use of canakinumab, predominantly administered every other month (Q8W) in the treatment of SchS, have been published [ACZ885 SchS Literature Review 2021]. In addition to the 20 patients reported in Study DDE03T, the literature review identified the following 25 patients with SchS who were treated with canakinumab:

- Two open-label single-treatment arm trials:
    - A 9-month open-label, single-treatment arm trial that evaluated canakinumab in patients with SchS (de Koning et al 2013; 8 patients). All patients received canakinumab 150 mg s.c. monthly for 6 months, followed by a 3-month observation period. Eight patients (51-75 years, mean 64 years) enrolled in the study at a single academic centre. The primary outcome for this study was defined as complete or clinical remission at Day 14, with secondary outcome measures of prevention of

disease relapse, PGA and patient global assessment of disease activity, changes in inflammatory markers (CRP, SAA), quality of life, time to disease relapse after the last dose of canakinumab, safety and tolerability.

    - A prospective IIT aimed at evaluating if canakinumab, administered s.c. 150 mg Q8W, could induce and maintain clinical remission in patients with SchS. Of the 4 patients screened, 1 patient qualified for the study (Vanderschueren and Knockaert 2013, Betrains et al 2020; 1 patients). The male patient reported a 2-year history of recurrent fever with headache and malaise, typical skin rash, bone pain, and arthralgias, accompanied by a systemic inflammatory response and a monoclonal IgM kappa (5.2 g/L) paraproteinemia and was diagnosed with SchS at the age of 37 years. He was previously treated with anakinra 100 mg s.c. daily, which induced immediate symptomatic relief and a normalization of CRP and ESR levels.

- A national, cross-sectional observational study conducted in France over a 2-year period (January 2011 to January 2013) to record the off-label use of IL-1 agents in the treatment of autoinflammatory diseases (Rossi-Semarano et al 2015; 1 patients). The cross-sectional observation study contained data on both anakinra and canakinumab treatment. Of the 7 patients diagnosed with SchS, 6 patients were treated with anakinra and 1 patient was treated with canakinumab. The median age was 55.3 years and the median disease duration was 7.4 years at time of anti-IL-1 treatment onset.
- A retrospective analysis of an Italian multicenter cohort in patients with SchS (Crisafulli et al 2020; 5 patients). Clinical data of 24 patients from 9 centers (median follow-up 6 years; median age at diagnosis 56.5 years; median diagnostic delay was 2 years) were collected. Therapeutic responses were evaluated in 20 patients. In 7 of the 14 patients initially treated with **anakinra**, this therapy was continued with benefit. In the other 7 patients the treatment with anakinra was discontinued, with 5 patients switching to treatment with **canakinumab**.
- Six case reports or case series of patients with SchS treated with **canakinumab**: Thomsen et al (2011) (1 patient), Gladue et al (2014) (2 patients), Pesek and Fox (2014) (2 patients), Gorodetskiy et al (2018) (1 patient), Salugina et al (2020) (3 patients plus 1 previously reported in Gorodetskiy et al (2018)) and Curi et al (2020) (1 patient).

When treated with canakinumab, 44 patients (including the 20 patients from Study DDE03T) showed a clinical response (n=35 complete or n=9 partial). One additional patient died and was not considered for clinical response (Crisafulli et al 2020).

Table 3 Summary of additional patients treated with canakinumab in literature

Reference	Sex	Age (y)	Disease duration (y)	Previous IL-inhibitor treatment	CAN dose	CAN responder[1]	Relapse
de Koning et al (2013) N=8	M	66	14	anakinra	150 mg Q4W for 6 m with 3 m observation period	Response evaluation at Day 14: Complete*: n=6/8 Clinical**: n=2/8;	Within 3 m
	F	67	2.5	anakinra			Within 3 m
	M	51	6	anakinra			SAE (traffic accident, fatal outcome)
	M	63	20	anakinra			Within 3 m
	M	67	10	anakinra			Several months later
	M	75	17	anakinra			Several months later
	F	63	25	anakinra			Within 3 m
	M	59	9	anakinra			Relapse at Day 27, second dose of CAN induced clinical remission, symptoms reappeared at Day 37, discontinued at Day 39
Vanderschueren and Knockaert (2013) / Betrains et al (2020) N=1	M	41	4	anakinra	150 mg Q8W; in case of improvement without clinical remission, add. 150 mg could be added with subsequent dosing increased to 300 mg Q8W; in case of recurrent flares, dose interval could be reduced to 4 wk	Complete	Per protocol, after 28 wk of treatment, CAN was interrupted after four injections. 10 wk after the treatment pause, high fevers, headache, joint pain, and urticarial rash recurred to an incapacitating degree. CAN was resumed with prompt response.
Rossi-Semerano et al (2015) N=1	NR	NR	NR	anakinra	150 mg Q8W	Partial	NR
Crisafulli et al (2020) N=5	NR	NR	2 (median) - 24 pts	anakinra	NR	Complete response in 3 pt, partial response in 1 pt, 1 pt had a fatal outcome (multiple myeloma)	NR
Thomsen et al (2011) N=1	F	51	8	anakinra	Dose NR; administered twice during a 2 wk period	Partial	Relapse of bone pain, arthralgias, faint rash accompanied by tiredness and suspected fever
Gladue et al (2014) N=2	M	58	<2	anakinra	150 mg Q8W switched to Q4W	Partial	3 days following his fourth injection, pt had a fatal ventricular tachycardia arrest (pre-existing cardiac disease with pacemaker reported)
	F***	44	NR	anakinra	150 mg Q8W switched to Q4W	Complete	Continues to be asymptomatic until the day of injection when pt occasionally presents with one to two urticarial lesions
Pesek and Fox (2014) N=2	M	63	1	No	150 mg Q8W; increase of dosing interval to 3-4 m	Complete	No
	F	47	7	No	150 mg Q8W	Complete	Worsening of arthralgia (corticosteroid withdrawal considered the cause)
Gorodetskiy et al (2018) N=1	M	44	4	No	150 mg Q8W; increase of dosing interval to every 3-4 m	Complete	No
Curi et al (2020) N=1	M	48	1.5	No	150 mg Q8W	Complete	No
Salugina et al (2020) N=4 (incl 1 patient from Gorodetskiy et al 2018)	M****	51	11	No	150 mg Q8W	Complete	NR
	NR	36	7	No	150 mg Q8W	Complete	NR
	NR	58	5	anakinra	150 mg Q8W	Complete	NR
	NR	69	3	anakinra	150 mg Q8W	Complete	NR

CAN, canakinumab; F, female; M, male; m, month; NR, not reported; pt, patient; wk, week; y, year.
Summary of additional patients treated with canakinumab in literature, excluding the 20 patients reported in Study DDE03T.
*For de Koning et al (2013), complete response defined as a PGA of disease activity of 0 to 1 (no or minimal symptoms/signs, including rash) with normal CRP (≤10 mg/L).
**For de Koning et al (2013), clinical response defined as absent or minimal disease activity and a greater than 75% improvement of CRP levels from baseline, although still above 10 mg/L.
*** Patient presented with signs and symptoms consistent with SchS but with the continued absence of monoclonal gammopathy.
**** Same patient as reported in Gorodetskiy et al (2018).
[1] As determined by the treating physician

CHMP comment

The applicant submitted a review of the scientific literature of canakinumab, anakinra and rilonacept used in additional 25 patients with SchS. The described small studies, analyses and case reports indicate effectiveness of anti-IL-1 treatment in controlling signs and symptoms of SchS with the majority of patients achieving complete clinical response. However, due to rarity of the disease the number of the patients was low (n=25) and the data are limited.

4.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Schnitzler Syndrome (SchS) is a rare disease and the exact prevalence is unknown (<1 per 1,000,000). Therefore, only one randomized, placebo-controlled trial has been conducted in patients with SchS.

Study DDE03T was a Phase 2, multicentre, randomized, double-blind, placebo-controlled, investigator initiated trial (IIT) that evaluated safety and efficacy of canakinumab in SchS patients. The study was conducted in 4 centres in Germany. The study consisted of 4 Parts (A, B, C and D).

Part A was a 7-day double-blind, placebo-controlled study of a single SC dose of canakinumab 150 mg. Patients were randomly assigned to receive canakinumab or placebo. 7 patients were in the canakinumab group and 13 patients received placebo. The applicant explained the difference in group sizes due to inadvertent imbalance in study drug distribution between study centres. However, the submitted information regarding randomization and study drug distribution is insufficient and needs to be further clarified. (MO)

At Day 7, patients were unblinded and moved to the open-label phase of the study (Part B, C and D). Part B was a 16-week open-label follow-up phase to optimise the canakinumab dose. Based on Physician's Global Assessment (PGA) patients with a complete clinical response received 150 mg upon confirmed relapse. Partial responders to canakinumab 150 mg received canakinumab 150 mg on Day 7 and were given canakinumab 300 mg upon relapse, while Non-responders had to be discontinued to receive standard of care treatment. Patients from the Placebo group who had no clinical response received the first canakinumab 150 mg dose on Day 7. Complete responders continued to receive canakinumab 150 mg upon subsequent relapses, partial responders received another 150 mg dose at Day 14 and 300 mg upon subsequent relapses. All patients who switched to canakinumab therapy from placebo showed clinical improvement, as indicated by reductions in PGA total scores.
All patients who successfully completed Parts A and B were eligible to enter the 4-year open-label extension phase i.e. Part C and D.
Part C of the study (1 year), patients were taking either canakinumab 150 mg or 300 mg based on previous individual responses in Parts A and B. Canakinumab was administered upon confirmed relapse of symptoms.
In Part D (3 years) canakinumab was given as needed based on previous responses in Part C (individual mean dosing intervals) to ensure a constant low disease activity and low inflammatory markers. Relapse of symptoms was not required for canakinumab dosing during Part D.

20 patients were enrolled. 45% (n=9) were female and 55% (n=11) were male patients. Different values for the median age were reported in the reports of the dossier and should be clarified by the applicant. The median duration of disease was 5.5 and 6.3 years, respectively, ranging from 1.5 years to 22 years. The majority of patients presented with symptoms of fatigue, myalgia and arthralgia/bone

pain at baseline, and all patients had urticarial rash and monoclonal paraproteins (mainly IgM) as major diagnostic criteria prior to enrolment.

All patients had a delay between Part B and Part C ranging from 33 to 300 days due to the protocol amendment for the open-label extension part of the study. The MAH states that on Day 0 no administration of the study drug took place. Therefore, the first dosing interval in Part C of the study is considered not representative as patients had different delays before starting Part C.

Efficacy data and additional analyses

Currently, the assessment of efficacy from this study is compromised by the lack of appropriate documentation according to ICH standards, including statistical analyses and results (MO), and the unclear circumstances related to randomisation and study drug distribution (MO). Therefore, at this stage, the assessment is only preliminary, pending answers to the MOs.

The study met its primary endpoint.

The results show a higher proportion of patients with complete clinical response in the canakinumab-treated group with 71.4% (n=5/7) compared to 0% in the placebo group (n=0/13) at Day 7 (p=0.001). Additionally a decrease in disease activity (PGA) was observed from baseline in the canakinumab-treated group (p=0.018). The difference in median changes in PGA total scores was canakinumab group -11 vs. placebo group 0 with p<0.0001.

In Part B all patients who switched from placebo to canakinumab treatment showed clinical improvement, as indicated by reductions in PGA total scores. In this 16-week period, relapse of clinical symptoms was reported in 14 patients, who subsequently received 1 to 3 additional canakinumab injections. Eight patients with complete clinical response and normalized CRP levels 7 days after canakinumab treatment initiation in Part B continued with canakinumab 150 mg doses. Twelve patients received canakinumab 300 mg doses because of slightly elevated inflammatory markers and/or remaining mild to moderate disease activity after canakinumab 150 mg initiation.

The results from all parts show that the mean PGA decreased from 14.5 at baseline to 4 at month 57. However, it has to be noted that the number of participants also decreased in this time period from 20 to 15. At the beginning of Part C the mean PGA was 9 at month 6. In the following month the values varied between 9 (highest) and 4 (lowest).

In the canakinumab-treated group, median serum levels of CRP decreased from 9.3 mg/dL at baseline to 0.6 mg/dL at Day 7 (p=0.031). Median SAA levels also decreased from 428 mg/L to 13 mg/L (p=0.031). The low levels of the inflammation markers were maintained during the open-label phase. All but 5 patients reached CRP levels within the reference level.

The recommended Q8W dosing regimen has not been tested in study DDE03T. The sponsor claims that the median canakinumab dosing intervals during the open-label extension phase of Study DDE03T were with 62 days (150 mg) and 63 days (300 mg) comparable to the 8-week dosing regimen proposed for SchS. However, the data show that the dosing intervals over the whole study ranged from 28 days to at least 1 year. Therefore, it is not clear, if the safety results would be similar, especially for patients without a relapse and canakinumab administration in 12 month. In Part B 20% of patients were without a relapse for 16 weeks and in Part C 17.6% of patients were without a relapse for 12 month. The MAH discussed the proposed posology and revised the wording. With the change of the posology and the more flexible dosing regimen with a minimum of every 4 weeks the results for long-term efficacy of patients in need of shorter dosing intervals could be similar to the results of the study. However, due to the high percentage of patients, who were without study drug administration in 12 month, it remains unclear whether the recommended dosing interval would change the benefit/risk

ratio of the dosing regimen evaluated in this study. Furthermore no information on patients with longer dosing intervals has been included in the PI. (MO)

The applicant also submitted a review of the scientific literature of canakinumab, anakinra and rilonacept used in additional 25 patients with SchS. The described small studies, analyses and case reports indicate the effectiveness of anti-IL-1 treatment in controlling signs and symptoms of SchS with the majority of patients achieving complete clinical response. However, due to rarity of the disease the number of the patients was low (n=25) and the data are limited.

4.4.4. Conclusions on the clinical efficacy

The data from Study DDE03T submitted provide signals of efficacy. Canakinumab administration reduced the clinical signs and symptoms of SchS (5/7 patients had complete clinical response in the canakinumab-treated group compared to 0/13 patients in the placebo group at day 7). Furthermore, inflammatory marker levels have been reduced measured by CRP and SAA and overall quality of life measured by DLQI and SF-36 improved. Results from the long-term extension phase (>4 years) indicate long-term efficacy of canakinumab in patients with SchS at a dose of 150 mg or 300 mg.

However, Major Objections have been raised.

The main issues are whether the study has been conducted such that the results can be considered accurate and reliable, and whether the level and quality of the documentation provided in the dossier can be considered fit for purpose for a regulatory submission. The scant details provided in the publication and Module 2 documents do not provide a sufficient basis for an adequate assessment.

The MAH should re-analyse the data using appropriately selected and duly documented statistical methods and subsequently compile a full ICH E3 -compliant CSR to support the conclusions made in corresponding Module 2 documents. (MO)

The number of patients was very limited and the randomization in Part A (double-blind, placebo controlled phase) was unbalanced with only 7 patients being randomized to the canakinumab group. The submitted information regarding randomization is insufficient. Until the unclear circumstances around randomisation and treatment arm assignment in the efficacy analyses are clarified, it cannot be overall agreed that the presented results truly reflect the efficacy of canakinumab.

Furthermore, the proposed wording of the posology according to the SmPC is still considered not justified. (MO)

4.5. Clinical safety

Introduction

Product

Canakinumab is a high-affinity human anti-human-IL-1β monoclonal antibody that belongs to the IgG1 kappa isotype subclass with a half-life of 26 days. Canakinumab specifically binds human IL-1β and blocks the interaction of IL-1β with the IL-1R, leading to inhibition of its downstream inflammatory targets (e.g., IL-6, CRP, CC-chemokine ligand 2 [CCL2]), thereby preventing IL-1β-induced gene activation and the production of inflammatory mediators.

Authorized indication

Canakinumab (Ilaris®) is approved for the treatment of CAPS, gouty arthritis in adults, Still's disease

including AOSD and Systemic Juvenile Idiopathic Arthritis (SJIA), and periodic fever syndromes (Tumour necrosis Factor Receptor-associated Periodic Syndrome [TRAPS], Hyper-immunoglobulin D Syndrome [HIDS]/Mevalonate Kinase Deficiency [MKD], Familial Mediterranean Fever [FMF]).

Safety Data

Main study

- **Study DDE03T (ILESCH)** was randomized, double-blind, placebo-controlled study of canakinumab in 20 patients with SchS.

Supportive safety data

- Supportive clinical trial safety data from adult CAPS and AOSD patients
- Clinical safety data from patients with post-myocardial infarction that show a similar age range like patients with SchS
- Data are further expanded with data from post-marketing use of canakinumab and literature review of the use of canakinumab (and other IL-1 inhibitors) in the treatment of SchS.

20 patients were treated within the intended indication of SchS. The whole safety data base in this submission includes a total of ~6900 patients that were treated with canakinumab. The majority of patients within the safety data set origins from patients with post-myocardial infarction.

CHMP comment
The safety data from Study DDE03T are limited, which is reasonable due to the rarity of the disease. Therefore, the applicant submitted supportive safety data from patients from other indications (i.e. CAPS, AOSD and post-myocardial infarction) treated with canakinumab. In summary the whole data base includes data from ~6900 patients.

Patient exposure

The **SchS dataset** is based on **Study DDE03T**, a randomized, placebo-controlled, double-blind phase II trial in 20 adult patients with SchS consisting of 4 parts.

A) a 7-day double-blind, randomized, placebo-controlled single dose treatment of canakinumab

B) a 16-week open label follow-up-phase, with canakinumab treatment (150mg or 300mg) upon disease relapse

C-D) a 1 and 3-year open label extension study resulting a total follow-up of 4 years.

A detailed description of the study can be found in 5.4.2.

Demographics and baseline characteristics

The percentage of women was slightly higher in the canakinumab group (57%) than in the placebo group (38%). At baseline, markers of systemic inflammation (CRP and SAA) were elevated in both groups, with somewhat higher median CRP values in the canakinumab group (Krause et al 2017). Other baseline demographic and clinical characteristics were similar across the study groups. All patients were white and the median disease duration was 5.5 years (range, 2-22 years).

For additional details on the scientific reasoning followed by the rapporteurs on this point, including figures and tables, please refer to Krause et al 2017.

CHMP comment
This is the only study in patients of the target population within this safety data set. The number of patients (n=20) is very limited. Inclusion criteria are adequately set to define an appropriate patient population. Given the very low incidence and prevalence of the disease the number of patients included the DDE3T trial is reasonable. 75% percent of the patients completed the 4 years extension period.

The MAH provided a revised table summarizing the patient characteristics for each of the 20 patients included in the study in the D121 response.

Supportive data

The supportive **CAPS dataset** contains a pooled safety population of 125 adult patients and 69 children consisting of a total of 5 clinical trials (**A2102**, **D2201**, **D2304**, **D2306** and **D2308)**. For the safety data set AEs and SEAs are only used for the adult population. The mean duration of exposure in the CAPS population is stated with 507.3 days (range 29-1884 days).

Supportive **AOSD dataset** consists of a randomized, double-blind placebo-controlled phase II study for patients with AOSD (**GDE01T).** The majority (85.7%) of patients in the canakinumab treatment group were exposed to canakinumab for ≥ 12 weeks with a mean exposure of 106 days.

The supportive dataset of patients with **post-myocardial infarction** includes the majority of patients within the whole safety data set for this application (total: 10,061; treated: 6,718; placebo: 3,344) from a phase III trial in patients with prior myocardial infarction (MI) with inflammatory atherosclerosis (**M2301)**. The mean treatment exposure for all treatments (50, 150, 300 mg) was 3.12 years (range: 0.01-5.71 years). The median age of patients in the study was 61 years.

CHMP comment
The CAPS and AOSD data set includes patients with a similar disease with regard to clinical presentation and proposed pathology as compared to SchS which shows however a different age range. Safety data for CAPS and AOSD are thus considered supportive for the safety assessment. Patients with post-myocardial infarction was chosen as supportive data by the MAH since the range of age is similar to SchS.

Adverse events

AEs in SchS dataset

No AEs were reported in Part A (7 days) of study DDE3T. A total of 15 (75%) patients experienced at least one AE in the 16 week follow up phase Part B. The most frequently reported AEs by SOC (≥ 20% patients) were infections and Infestations (9 patients, 45.0%) and Musculoskeletal and connective tissue disorders (4 patients, 20.0%). The most frequently reported AE by PT in study Part B was influenza (6 patients, 30%).

All 17 patients (100%) who entered Parts C and D had at least one AE during the 4-year open-label extension of the study. The most frequently (≥30% patients) reported AEs by SOC were Infections and infestations (17 patients, 100%), Musculoskeletal and connective tissue disorders (14 patients, 82.4%) and Gastrointestinal disorders, Skin and subcutaneous tissue disorders and Injury poisoning and procedural complications (each with 6 patients, 35.3%).

The most frequently reported AEs by PT in Parts C and D (≥15% patients) were nasopharyngitis (11 patients, 64.7%), osteoarthritis and hypertension (each with 4 patients, 23.5%), tachycardia,

bronchitis, cystitis, respiratory tract infections, urinary tract infection, back pain, abdominal pain upper, eczema (all 3 patients each, 17.6%).

Severity and relation to study treatment

The majority of AEs in all parts of the study were assessed as mild or moderate in severity with few severe AEs. The majority of AEs in all parts of the study were assessed as not related or unlikely related to study drug. Still, there were two serious AEs (pneumonia and sepsis), which were reported as SAEs. One SAE (sepsis) was fatal.

Relation to study treatment

The majority of suspected AEs were resolved and only few were ongoing at the end of study. Infections and infestations were the most commonly reported AEs suspected to be related to study treatment.

Table 4 Treatment-emergent AEs by PTs regardless of relationship to treatment in Study DDE03T-Part B

Preferred terms	Total N=20 n (%)
Number of patients with at least one AE*	**15 (75.0)**
Influenza	6 (30.0)
Gastrointestinal disorder	1 (5.0)
Gastrooesophageal reflux disease	1 (5.0)
Acarodermatitis	1 (5.0)
Bacterial disease carrier	1 (5.0)
Bronchitis	1 (5.0)
Nasopharyngitis	1 (5.0)
Tooth infection	1 (5.0)
Chillblains	1 (5.0)
Aspartate aminotransferase increased	1 (5.0)
Vitamin D decreased	1 (5.0)
Arthralgia	1 (5.0)
Back pain	1 (5.0)
Musculoskeletal pain	1 (5.0)
Osteochondrosis	1 (5.0)
Dysuria	1 (5.0)
Leukocyturia	1 (5.0)
Asthma	1 (5.0)
Cough	1 (5.0)
Oropharyngeal pain	1 (5.0)
Rash	1 (5.0)
Rosacea	1 (5.0)
Hypertension	1 (5.0)

Preferred terms	Total N=20 n (%)
* A patient with multiple AEs is counted only once in the "Number of patients with at least one AE" row. A patient with multiple AEs within a preferred term is counted only once for that preferred term. MedDRA Version 21.0 has been used for the reporting of AEs. Source: [Study DDE03T Suppl01-Table 14.3.1-1.1a]	

Table 5 Treatment-emergent AEs reported in more than 1 patient, by PT regardless of relationship to treatment in Study DDE03T-Parts C and D

Preferred terms	Total N=17 n (%)
Number of patients with at least one AE*	**17 (100)**
Nasopharyngitis	11 (64.7)
Osteoarthritis	4 (23.5)
Hypertension	4 (23.5)
Tachycardia	3 (17.6)
Bronchitis	3 (17.6)
Cystitis	3 (17.6)
Urinary tract infection	3 (17.6)
Back pain	3 (17.6)
Eczema	3 (17.6)
Respiratory tract infection	3 (17.6)
Abdominal pain upper	3 (17.6)
Conjunctivitis	2 (11.8)
Tinnitus	2 (11.8)
Gastroenteritis	2 (11.8)
Vertigo	2 (11.8)
Gastrointestinal infection	2 (11.8)
Pyrexia	2 (11.8)
Pulpitis dental	2 (11.8)
Sinusitis	2 (11.8)
Upper respiratory tract infection	2 (11.8)
Arthralgia	2 (11.8)
Night sweats	2 (11.8)
Intervertebral disc protrusion	2 (11.8)
Basal cell carcinoma	2 (11.8)
Benign prostatic hyperplasia	2 (11.8)
Cough	2 (11.8)

*A patient with multiple AEs is counted only once in the "Number of patients with at least one AE" row.

A patient with multiple adverse events within a preferred term is counted only once for that preferred term

MedDRA Version 21.0 has been used for the reporting of AEs

Source: [Study DDE03T Suppl01-Table 14.3.1-1.1b]

CHMP comment

Treatment emergent AEs by SOC during the study mostly consisted of infections and Infestations and Musculoskeletal and connective tissue disorders. No AEs were observed during part A of study (1 week). During part B (16 weeks) 6 cases of influenza (30%) occurred that can be mostly attributed to the winter flu season (September-March). Nasopharyngitis was most common (64.7%) during the extension phase of the study (4 years).

Supportive data

AEs in CAPS data set (A2102, D2201, D2304, D2306 and D2308)

Most prominent AEs by SOC in CAPS patients 18-59 years were Infections and infestations (75.2%), Musculoskeletal and connective tissue disorders (49.6%), Nervous system disorders (43.4%), Gastrointestinal disorders (42.5%) and Respiratory, thoracic and mediastinal disorders (31.9%). Nasopharyngitis occurred in 37.2% percent of patients. The same trend was observed in CAPS patients ≥60years. However, still the number of patients within this group which better reflects the ageing of the SchS population is limited.

AEs in AOSD data set

The most commonly reported AEs in the canakinumab group by SOC (≥20% patients) were Musculoskeletal and connective tissue disorders (7/21, 33.3%) and Gastrointestinal disorders and Infections and infestations (both 6/21, 28.6% each).

AEs in post-myocardial infarction data set (M2301)

A total of 8744 (86.9%) patients had at least one AE during the study. The most common AEs by SOC were Infections and infestations (51.2%), Musculoskeletal and connective tissue disorders (35.8%) and Gastrointestinal disorders (31.4%). The most common AE by preferred term in the combined canakinumab group was viral upper respiratory tract infection (13.1%), Hypertension (10.2%), Angina pectoris (8.4%), Back pain (8.4%), non-cardiac chest pain (8.1%), arthralgia (8.0%), and upper respiratory tract infection (8.0 %). No obvious difference between canakinumab-treated and placebo patients can be observed. Common AEs are most likely attributed to the underlying cardiovascular disease of the patients and age-associated comorbidities, while canakinumab treatment may have an influence on the rate of infections based on the MOA of the antibody. Overall AEs within this data set appear to be similar as compared to the safety data set for patients with SchS.

Adverse events of special interest within the safety data set

- **Infections (including opportunistic infections)**

In the **SchS data set** (study DDE03T) 9/20 patients (45%) during Part B and all 17 patients in Parts C and D experienced at least one event in the Infections and infestations SOC. A single patient may have experienced more than one AE of infection.

In Part B (over 16 weeks), 9 patients experienced 12 AEs of infection. Six patients contracted influenza (one who had two bouts and one who also had nasopharyngitis). Additional infections included one patient who had bronchitis, one tooth infection, one Acarodermatitis, and one Bacterial disease carrier. All respiratory infections except one occurred between the months of September and March each year during the study (winter flu-season). All 12 infections were reported as non-serious and were considered mild (8 events), moderate (3 events) or severe (1 event of influenza). Eleven of the 12 infections resolved, with the exception of one event of (mild) bronchitis reported as outcome unknown. All 12 AEs of infection were considered unlikely related to canakinumab by the investigators.

In Parts C and D (over a 4-year period), respiratory tract infections were also the most frequently reported infection (15 of 17 patients; 88.2%). Patients frequently experienced more than one

respiratory tract infection; 11 patients (64.7%) developed nasopharyngitis (all reported as common cold), and 9 patients developed events of; bronchitis (3 patients), respiratory tract infection (3 patients), upper respiratory tract infection (2 patients), sinusitis (2 patients), or pneumonia (1 patient). Patients frequently experienced more than one respiratory tract infection. Urinary tract infections were reported in 5 patients (29.4%) (cystitis in 2 and UTI in 2 patients and one patient with both cystitis and UTI). Four patients (23.5%) reported infections of the GI tract. Infections during Parts C and D were non-serious except one case of pneumonia described in Section 2.1.3) and were mild in the majority of cases. Causality was reported as probable or possible for infections in 6 of the 17 patients (including pneumonia).

One patient died during the study due to sepsis.

CHMP comment
Infections are a known risk associated with the treatment of canakinumab. The MAH concludes that infections reported in Study DDE03T are consistent with the known safety profile, since the majority were of the respiratory tract, mild and resolved. This conclusion can be considered acceptable since occurrence of infections is also comparable between the SchS and the other patient populations used for this application.

However, there were 2 severe adverse events with suspected relationship to canakinumab that occurred during the trial, one with a fatal outcome (sepsis). This one case is of significant importance given the overall low number of SchS patients (n=20) that was initially included in this trial. The MAH provided additional information on this case in the D121 response that raised further concerns and questions with regard to the treatment of this patient.

Supportive data set

In adult patients (18 to <60 years) of the **CAPS dataset**, the most frequently reported AEs by SOC were Infections and infestations (75.2%). In adult patients ≥60 years old, the most frequently reported AEs by SOC were Infections and infestations (50%).

In the **AOSD dataset**, infections and infestations, the most common previously identified AEs as a result of canakinumab treatment, were well balanced across the 2 groups, with 47.6% of canakinumab-treated patients and 46.7% of placebo-treated patients reporting at least one infection. Review of all infection events identified four potential opportunistic infections in the study population.

In patients with **post-myocardial infarction** (study M2301) the most frequently reported AEs by SOC were Infections and infestations (51.2%). Of the infection events adjudicated by an independent adjudication committee, 10 were confirmed as opportunistic infections.

- **Malignancy**

During the study **DDE03T**, no events of malignancy were recorded in Parts A or B. In Parts C and D, five patients reported an event within the Neoplasms benign, malignant and unspecified. Basal cell carcinoma occurred in 2 patients and Bowen's disease in a further one; both were considered non-serious by the investigator and excised. Colon adenoma (excised), uterine leiomyoma (excised), and melanocytic naevus (excised) were reported in one patient each and are non-malignant conditions frequently seen in the general population. Multiple myeloma (PT: Plasma cell myeloma) occurred in one patient and led to study discontinuation during Part D.

Of the events within the Neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC in DDE03T, one represented a malignant event. The event multiple myeloma (plasma cell myeloma) was

diagnosed 16 years after initial diagnosis during routine haemato-oncologic surveillance, and was reported as unrelated to canakinumab but rather due to underlying disease.

CHMP comment
The evaluation on malignancy by the MAH is considered acceptable.

Serious adverse event

SAEs within the SchS dataset

No SAEs were reported in the 7-day placebo-controlled phase of the study (Part A).

During the 16-week open-label phase (Part B), 3 SAEs were reported in two patients, which include: two SAEs of hypertension, one SAE of severe lumbago (back pain).

During Parts C and D (long-term extension phases), a total of 7 SAEs were reported, of which 2 were suspected to be related to canakinumab treatment by the Investigator.

The patient experienced a suspected cerebrovascular accident (CVA), cranial nerve III paresis, pneumonia and tonsillitis requiring hospitalization. The events (CVA, cranial nerve III paresis, pneumonia) resolved. The investigator considered the events suspected to be related to the study medication.

CHMP comment
The conclusion that the events (cerebrovascular accident, pneumonia) are related to the study treatment is acceptable.

One patient died during the study due to sepsis (See Section Death for further details).

CHMP comment
This case is extensively assessed under section 'Death'.

Table 6 Treatment-emergent SAEs in Study DDE03T

PTs as per SAE CIOMS narrative	Relationship of AEs to the study drug *	Event Outcome	ACZ885 dose (mg)	Time to onset after first dose
Part B				
Hypertensive crisis	Not suspected	Recovered	150	3 months
Sciatica	Not suspected	Recovering	150	6 weeks
Parts C and D				
Pneumonia Cerebrovascular accident IIIrd nerve paresis	Suspected	Recovered	150	6.5 months
Atypical mycobacteriosis Sepsis	Suspected	Fatal **	300	10 months
Inguinal hernia	Not suspected	Recovered	150	1.5 years
Plasma cell myeloma	Not suspected	Not recovered **	150	3 years
Bile duct stone	Not suspected	Recovered Recovered	300	> 4 years
Uterine leiomyoma	Not suspected	Recovered	300	> 4 years
Craniocerebral injury Physical assault	Not suspected	Recovered	150	> 4 years
* Relationship to study drug applicable for all events in the PT column ** Patient discontinued study CIOMS Safety narratives [Study DDE03T Suppl01-CIOMS]				

5 SAEs were not suspected to be related to study drug by the Investigator (worsening of inguinal hernia, multiple myeloma (plasma cell myeloma), choledocholithiasis, leiomyoma and craniocerebral trauma due to assault).

One patient experienced inguinal hernia.

CHMP comment
The MAH concludes that the occurrence of the SAE is not suspected to be related to the study drug. The conclusion is considered acceptable.

One patient was diagnosed with multiple myeloma (plasma cell myeloma).

CHMP comment
The conclusion that a casusality with canakinumab and the development of plasma cell myeloma in a patient with SchS is not suspected is considered acceptable. According to the literature a main complications of the Schnitzler syndrome are the development of a lymphoproliferative disorder in about 15 to 20% of cases (Gusdorf and Lipsker 2017).

The patient was last reported in June 2021 as "not recovered" with a stable disease.

One patient presented with choledocholithiasis (bile duct stone), requiring cholecystectomy.

CHMP comment
The MAH concludes that the occurrence of the SAE is not suspected to be related to the study drug. The conclusion is considered acceptable.

One patient presented with skull contusion, fracture of ribs, strain of the cervical spine and contusion of the right knee.

CHMP comment
The MAH concludes that the occurrence of the SAE is not suspected to be related to the study drug. The conclusion is considered acceptable.

One patient was diagnosed with noncancerous growth.

CHMP comment
The MAH concludes that the occurrence of the SAE is not suspected to be related to the study drug. The conclusion is considered acceptable.

Supportive data

SAEs within the CAPS dataset

13 adult patients (11.5%) in the age group of 18 to 59 years and one patient (8.3%) ≥60 years had SAEs while on canakinumab treatment (Table 2-9). The most common SAEs were pregnancy, abortion induced, and headache (1.8% each).

SAEs within the AOSD dataset

Three SAEs occurred within the AOSD dataset in patients that were treated with canakinumab. No SEAs were observed in the placebo group. Translation of these observation in the whole safety population is limited due to the rather low number of patients (canakinumab: 21, placebo: 15).

SAEs within post-myocardial infarction dataset

Infections seem to be the most prevalent cause for SAEs besides adverse events that are more likely to be associated with the underlying cardiovascular disease and comorbidities. There is a notable slight increase of cases of sepsis in the combined canakinumab treated group as compared to placebo (1.2% vs. 0.8%). Beside that particular SEAs seem to be not increased as compared to placebo.

Deaths

Deaths within the SchS dataset

One death was reported during the trial with SchS patients (study DDE03T). One patient died during the study due to sepsis.

Based on this observation the RMP and SmPC were updated and opportunistic infections were upgraded from an Important Potential risk to an Important Identified risk in the risk management plan, with the associated addition of text relating to this risk in the Special Warnings and Precautions and Adverse Drug Reactions sections of the SmPC.

Narrative (excerpt) of a reported death under treatment with canakinumab in study DDE03T

[redacted in line with PPD protection legislation]One patient died during the study due to sepsis.

CHMP comment

One patient died due to sepsis.

Upon assessment of this case the MAH concluded that death due to sepsis is suspected to be related to the treatment with canakinumab. This conclusion is supported, in particular since the patient received the last two doses within a dosing interval of only 28 days. Based on the mode of action of canakinumab impaired IL-1 signalling can increase the susceptibility for infection, as IL-1ß is critical for host defence. This patient received the last 7 doses of 300mg canakinumab up to every 4 weeks. This potentially led to a continuous high systemic exposure (increased accumulation of canakinumab) with a strong suppression of the inflammatory IL-1 response in this patient increasing the risk for infection. However, PK data were not assessed.

Overall, this case is of concern and is assessed critically given the overall low number of SchS patients within the DEE3T study. The MAH provided additional information on this case in the D121 response including a tabular overview on clinical parameters assessed for each study visit that raised further concerns and questions on this case. It is so far unclear why the patient was dosed at the first visit of Part C and why the patient was treated with the shortest dosing interval of the entire DDE03T study despite no improvement in the relevant disease scores. Laboratory parameters were partially not reported during the last visits of this patient. Overall, questions on this case are not resolved (OC).

Supportive data set

Death within CAPS dataset and AOSD dataset

No death was reported

Deaths within post-myocardial infarction data set

Within the population of post-myocardial infarction a total of 1081 patients died. The number of deaths that were not associated with cardiovascular disease (non-CV death), adjudicated by the cardiovascular clinical events adjudication committee was for canakinumab as compared to placebo was 273 patients (1.08/100 patient-years) and 141 patients (1.12/100 patient-years), respectively.

The most common non-CV primary causes of death by the cardiovascular clinical events adjudication committee were malignancy, sepsis, respiratory failure, and infection.

Deaths due to sepsis were higher for the canakinumab groups as compared to placebo (0.15/100 patient-years, 0.21/100 patient-years and 0.16/100 patient-years for canakinumab 300 mg, 150 mg and 50 mg, respectively, vs.0.13 for placebo) with no apparent dose-dependency observed across the canakinumab doses.

CHMP comment
There is a slight trend for increased rates of infections and respiratory failures as well as to a low extent for sepsis.

The MAH provided more information on the death caused by sepsis within the D121 response and discussed the potential parallels of these cases within study M2301 and the fatal case of sepsis within study DDE03T. Overall, no clear connection can be drawn between the cases observed in study M2301 and the case of fatal sepsis in study DDE03T.

Laboratory findings

Laboratory evaluations data were not reported for Study DDE03T. However, data from similar populations (adult CAPS and AOSD) and from patients of a similar age profile (Study M2301) are supportive of the known safety profile of canakinumab.

Immunogenicity
No new immunogenicity information specific to the SchS patient population was generated for this submission.

Immunogenicity has not proved to be a significant concern for canakinumab. The incidence rates of anti-drug antibodies (ADA) and the risk of ADA-mediated consequences are separate entities. Based on the results from the integrated analysis of data presented in [ACZ885 Integrated Immunogenicity Report 2016], the incidence of anti-canakinumab antibody development during treatment in all indications is low (<3%), and no clinical consequences to these detected antibodies were evident. That is, there was no evidence of decreased canakinumab levels or target binding related to the development of ADA, and ADA were rarely associated with immunogenicity-related AEs. In addition, no anaphylaxis or anaphylactoid reactions were reported.

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

AEs leading to discontinuation within the SchS dataset

2 patients (10%) prematurely discontinued the study due to AEs. One patient discontinued the study during Part C, due to an SAE of fatal sepsis and another patient discontinued the study during Part D, due to an SAE of multiple myeloma (plasma cell myeloma). These cases are also described in the SAE section.

Supportive data

CAPS dataset
6 patients (3.1%), including adult and paediatric patients, discontinued the study treatment due to AEs in the CAPS dataset.

AOSD dataset
3 canakinumab-treated patients (14.3%) discontinued the study treatment due to AEs during the 12-week double-blind phase of the GDE01T study due to i) cerebral ischemia (later diagnosed with Whipple's disease instead of AOSD), ii) hepatotoxicity of moderate severity, and iii) exacerbation of Still's disease. No placebo-treated patients discontinued due to an AE.

Post-myocardial infarction dataset

727 patients (7.2%) permanently discontinued study treatment due to AEs across the canakinumab-treated groups ((300mg: 7.7%; 150mg: 7.2%; 50mg: 6.6%) during the double-blind phase of the M2301 study. 245 patients (7.3%) discontinued the study due to AEs in the placebo group.

Post marketing experience

Literature review
A review of the existing scientific literature for patients treated with canakinumab was conducted, by searching appropriate databases, to identify publications relevant to SchS (with a cut-off date of 31-Jan-2021). Since 2011, publications reporting on canakinumab treatment in SchS included 45 patients in a total of 11 studies, case reports or case series. Of the 45 patients, 26 had previously been treated with anakinra, which was discontinued before initiating canakinumab treatment.

Reported AEs of special interest by SOC were Infections and infestations disorders and neoplasms benign, malignant and unspecified (incl. cysts and polyps).

Three patients had a fatal outcome; the cause of death was not provided in two cases containing limited information, and the third case describes a fatal arrhythmia in a patient with pre-existing cardiac disease and a pacemaker.

CHMP comment
Literature was reviewed by the MAH with regard to the use of canakinumab in the treatment of SchS. Overall, the reported AEs followed the safety profile of canakinumab observed in the other trials within this safety data set. Three patients died, while no causative connection between the event and canakinumab treatment can be assumed based on the information provided in the scientific publications.

4.5.1. Discussion on clinical safety

In Study DEE03T a total of 20 patients with Schnitzler Syndrome were exposed to canakinumab doses of 150mg or 300mg. 15 patients (75%) completed the whole study period of 4 years and were given canakinumab injections as needed based on individual disease activity and response to treatment.

Supportive clinical safety data from 125 adult CAPS and 31 AOSD patients with a mean exposure to canakinumab comparable to the SchS patients were submitted by the applicant. Furthermore, the safety data base was expanded by a large number of patients (6,718 treated) with post-myocardial

infarction with a median age (61 years) and median treatment duration (3.12 years).
In addition, literature was reviewed by the MAH with regard to the use of canakinumab in the treatment of SchS. Including the 20 patients treated within the SchS safety data set, at total of 45 patients treated with canakinumab are described in the literature since 2011.

Treatment emergent AEs by SOC in SchS patients mostly consisted of infections and Infestations and Musculoskeletal and connective tissue disorders. No AEs were observed during part A of study (1 week). During part B (16 weeks) 6 cases of influenza (30%) occurred that can be mostly attributed to the winter flu season (September-March). Nasopharyngitis was most common (64.7%) during the extension phase of the study (4 years).

Five SAEs occurred during the DDE3T trial (SchS data set) for which no relation to the study drug can be concluded. Of note, during the extension phase of study, two SAEs (pneumonia and sepsis) occurred that were suspected to be related with the study drug. One SAE (sepsis) led to a fatal outcome. This case is of concern given the overall low number of SchS patients (n=20) that was initially included in this trial.

One patient died during the study due to sepsis. Within the D121 response the MAH provided additional information on this case that raised further significant concerns and questions on this case that are yet not resolved. Upon assessment of this case the MAH concluded that death due to sepsis is suspected to be related to the treatment with canakinumab. The MAH states that based on this observation the RMP and SmPC were updated and opportunistic infections were upgraded to an Important Identified risk in the risk management plan, with the associated addition of text relating to this risk in the Special Warnings and Precautions and Adverse Drug Reactions sections of the SmPC.

The submitted supportive data showed that most prominent AEs by SOC also in CAPS patients were Infections and infestations, Musculoskeletal and connective tissue disorders, Nervous system disorders. Similar AEs were observed in AOSD patients with Musculoskeletal and connective tissue disorders, gastrointestinal disorders and Infections and infestations being the most common AEs by SOC. SEAs associated with sepsis were seen at 1.2% in the post-myocardial infarction dataset (canakinumab combined). Incidence for fatal sepsis was also slightly increased in the data set of 6718 patients with post-myocardial infarction (0.17% in combined canakinumab-treated patients vs. 0.13% in placebo). Discussion on potential parallels between cases of sepsis within the post-myocardial infarction dataset and the case of fatal sepsis in the DDE3T trial was provided by the MAH in the D121 response.

Literature was reviewed by the MAH with regard to the use of canakinumab in the treatment of SchS. Overall, the reported AEs followed the safety profile of canakinumab already observed for the other trials within this safety data set. Of note, three patients died, while no causative connection between the event and canakinumab treatment can be assumed based on the information provided in the scientific publications.

4.5.2. Conclusions on clinical safety

The safety data base in the proposed indication and dose consists of 20 patients with SchS. The identification of new safety concerns arising from this new patient population is thus strongly limited.

Supportive safety data from 125 adult patients with CAPS, 38 patients with AOSD for which canakinumab is already approved and 6,718 canakinumab-treated post-myocardial infarction patients was submitted by the applicant. However, the acquired safety data are not completely transferable to SchS due to disease-specific unique pathomechanisms and/or different median age of the patient

population.

Adverse events by SOC that were increased in the SchS population mostly consisted of infections and Infestations being the most prominent throughout the extension phase of the DDE03T. Overall, adverse events observed seem to be consistent with the already known safety profile of canakinumab.

2 severe adverse events with suspected relationship to canakinumab occurred within the SchS population, one with a fatal outcome (sepsis).

Notably, occurrence of fatal sepsis seems to be generally increased after canakinumab treatment as a slight trend for increasing incidence SAEs caused by sepsis could be observed in the data set of 6718 patients with post-myocardial infarction (1.2% canakinumab vs. 0.8% placebo). Occurrence of fatal sepsis was also slightly increased (0.17% canakinumab vs. 0.13% in placebo). However, no obvious relation between these cases and the patient with fatal sepsis could be observed with regard to risk factors (e.g. age, weight and comorbidities) could be observed.

Overall, the safety data observed for SchS in the main study DDE03T appears to be consistent with the known safety profile of canakinumab. A main limitation is the low number of SchS patients that could be included in the trial due to the strong rarity of the disease. Safety data observed for SchS were similar to CAPS, AOSD and patients with post-myocardial infarction that were provided as supportive safety data. The occurrence of the case of fatal sepsis is potentially linked to the short dosing interval of 28 days for this patient. The case led to the upgrade of opportunistic infections as important identified risk in the RMP.

Additionally, the data of Study DDE03T show that the dosing intervals over the whole study ranged from 28 days to at least 1 year. Therefore, it is not clear, if the recommended Q8W dosing regimen would lead to similar safety results, especially due to the fact that several patients were without a relapse and thus without a canakinumab administration for at least 12 months. (MO)

In conclusion, given all provided information the safety data presented do not fully support the planned use of canakinumab in the proposed new indication.

4.5.3. PSUR cycle

PERIODIC SAFETY UPDATE REPORT (PSUR) was submitted at 18 August 2021

Period covered by67 this report: 01 Jul 2018 - 30 Jun 2021

The conclusion of the PSUR is that the review of information from all available sources revealed no clinically relevant increase in the frequency or severity of any of the important identified risks.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4.5.4. Direct Healthcare Professional Communication

NA

5. Risk management plan

The MAH submitted/was requested to submit an updated RMP version (13.0) with this application. The

(main) proposed RMP changes were the following:

The Risk Management Plan (RMP) was updated to reflect

- the label extension to include the treatment of adult patients with Schnitzler syndrome (SchS)
- removal of Gouty arthritis registry (ACZ885H2401) due to feasibility of completing the study,
- removal of study ACZ885GDE01T [as completed during EMEA/H/C/001109/II/0067 procedure, approved 30- Jan-2020] and
- the addition of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [Ilaris SDA 054.1 EPITT no: 19566 approved 12-Mar-2021] as an important potential risk.
- The RMP is also aligned with new RMP template version 6.3.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 12.0
Part I	SchS added as a proposed indication.
Part II	SI: Epidemiology section is updated with SchS SII: No change SIII: Clinical trial exposure is updated for SchS SIV: No change SV: No change SVI: No change SVII: Information on important identified risks of infection, opportunistic infections and important potential risk of malignancy updated, related to SchS. Also addition of DRESS as an important potential risk. SVIII: Summary of safety concerns is updated with DRESS as an important potential risk.
Part III	Removal of GA registry Study ACZ885H2401 and Study ACZ885GDE01T from pharmacovigilance plan. Inclusion of severe skin reactions for targeted follow up checklist.
Part IV	No change
Part V	Updated based on updated EU SmPC. Removal of GA registry ACZ885H2401 and Study ACZ885GDE01T from summary of risk minimization measures. Addition of DRESS as an important potential risk.
Part VI	Information on important identified risks of infection, opportunistic infections and important potential risk of malignancy updated, related to SchS. Also addition of DRESS as an important potential risk.
Part VII	Annex 1: Not applicable Annex 2: Updated with the removal of Study ACZ885GDE01T, Study ACZ885H2401, and Study ACZ885N2301. Annex 3: Updated with the removal of GA registry Study ACZ885H2401 Annex 4: Addition of target follow-up Severe Skin Reactions checklist for DRESS. Annex 5: Updated with the removal of ACZ885GDE01T study Annex 6: SchS added to patient reminder card Annex 7: MedDRA version is updated and search terms added for important potential risk DRESS. Annex 8: Updated to reflect RMP updates.

Clinical trial exposure was updated regarding Schnitzler syndrome

A total of 20 patients were randomized into the investigator initiated trial (Study ACZ885DDE03T [DDE03T]) and received at least one dose of study medication. All 20 patients completed Parts A and B of the study (7 days and 16 weeks, respectively). A total of 17 patients entered the open-label extension (Parts C and D), of whom 15 patients completed the entire open-label extension period of 4 years (Krause et at 2020).

Details of important identified risks, important potential risks and missing information have been updated regarding Schnitzler syndrome:

Infections were reported for all patients (n=17) in Study DDE03T over the >4 year observation period, and were consistent with the known safety profile of canakinumab, being that the majority were infections of the respiratory tract ('common cold'), mild and resolved. In consideration of the >4-year observation period, the rates of respiratory tract infection (particularly the common cold) are not in excess of that seen in the general population [ACZ885C2 SCS-Section 2.1.5].

In Study DDE03T, one patient had an **opportunistic infection**. This case led to the RMP risk of opportunistic infections being upgraded from an important potential risk to an important identified risk in the Ilaris RMP v 8.0, and associated addition of text relating to this risk in the Warnings and Precautions and Adverse Drug Reactions sections of the EU SmPC in 2014 [ACZ885C2 SCS-Section 2.1.5].

During Study DDE03T, one event of malignancy was reported. Multiple myeloma (plasma cell myeloma) was diagnosed during routine haemato-oncologic surveillance, conducted due to the known development of lymphoproliferative disorders in SchS, and was reported as unrelated to canakinumab but rather due to underlying disease. It is known that 15-20% of SchS patients develop lymphoproliferative disorders (including plasma cell myeloma), typically appearing more than 10 to 20 years after the first signs of the syndrome in most cases (Lipsker 2010) [ACZ885C2 SCS-Section 2.1.5].

Table 7 Part II SVIII.1: Summary of safety concerns

Important identified risks	Infections
	Opportunistic infections
	Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)
Important potential risks	Malignancy
	Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)
	Canakinumab – immunosuppressants combination therapy toxicity (for periodic fever syndromes and Still's disease)
	Macrophage activation syndrome (for Still's disease)
	Interactions with vaccines
	Pharmacodynamic interactions
	Interactions with drugs eliminated by CYP450 enzymes
	DRESS
Missing information	Pregnancy and nursing women
	Effects on growth (for periodic fever syndromes and Still's disease)

PRAC comment

Drug reaction with eosinophilia and systemic symptoms (DRESS) is added as a new important potential risk upon PRAC recommendation (EMA/PRAC/158909/2021, 12 March 2021) No new safety concern has been identified regarding new indication Schnitzler syndrome.

Table 8 Summary of pharmacovigilance and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Infections	Addressed in EU SmPC in: Section 4.3 (Contraindication), Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) and Section 4.8 (Undesirable effects-summary of the safety profile) Additional risk minimization activities: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction. Additional pharmacovigilance activities: Study G2403: SJIA Registry Study ACZ885H2401
Opportunistic infections	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Additional risk minimization activities: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study G2403: SJIA Registry
Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for Still's disease)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study G2403: SJIA Registry Study ACZ885H2401
Important potential risks		
Malignancy	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study G2403: SJIA Registry Study ACZ885H2401
Drug induced liver injury (DILI, hepatic transaminase and bilirubin elevations) (for periodic fever syndromes and gouty arthritis)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Study G2403: SJIA Registry
Canakinumab – immunosuppressants combination therapy toxicity	Addressed in EU SmPC in: Section 4.4 (Special warning and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study G2403: SJIA Registry
Macrophage activation syndrome	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) Additional risk minimization activities: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: Study G2403: SJIA Registry MAS Adjudication Committee
Interactions with vaccines	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) and Section 4.5 (interaction with other medicinal products and other forms of interaction) Additional risk minimization activities: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Study ACZ885H2401
Pharmacodynamic interactions	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use) and Section 4.5 (interaction with other medicinal products and other forms of interaction)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Interactions with drugs eliminated by CYP450 enzymes	Addressed in EU SmPC in: Section 4.5 (Interaction with other medicinal products and other forms of interaction)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Addressed in EU SmPC in: Section 4.4 (Special warnings and precautions for use)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Missing information		
Pregnancy and nursing women	Addressed in EU SmPC in: Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization activities: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study G2403: SJIA Registry Study ACZ885H2401
Effects on growth	No risk minimization measure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study G2403: SJIA Registry

PRAC comment

The above table has been updated regarding addition of a new important potential risk DRESS and regarding removal of Gouty arthritis registry (ACZ885H2401, rationale see below) and removal of completed study ACZ885GDE01T. The updates are endorsed.

10.2.3 Study Registry H2401

Novartis proposes the removal of Gouty arthritis registry (ACZ885H2401) due to feasibility of completing the study. Novartis will continue to closely monitor exposure in these patients as required by routine pharmacovigilance and safety monitoring.

PRAC comment

The proposal of the MAH to remove the registry H2401 as an additional pharmacovigilance activity is endorsed for the reasons explained above. The MAH committed to continue to closely monitor exposure in these patients as required by routine pharmacovigilance and safety monitoring.

The summary of Risk Management plan has been updated accordingly.

All tables have been updated regarding the removal of Gouty arthritis registry (ACZ885H2401) and of completed study ACZ885GDE01T.

The Annexes have been updated accordingly.

In Annex 4 *Targeted Follow-up Checklist* a section regarding *Severe Skin Reactions* was included.

5.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

6. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to include information on the extension of indication related to the treatment of adult patients with Schnitzler's syndrome. The Package Leaflet (PL) is updated accordingly.

Changes were also requested to the PI to bring it in line with the current QRD template version.

Please refer to Attachment 1 which includes all agreed changes/comments to the Product Information.

The response document (section 5.1.1 to 5.1.2 and 5.1.4 to 5.1.5 as well as 6.1.1 to product information) submitted in March 2022 is in general acceptable. The marketing authorisation holder implemented adequately most of the requested changes, except one.

With regard to this particular case, it should be pointed out that in the meantime the EMA was consulted in order to confirm if the changes related to the guidance on the HPRA website should be mirrored as amendments of the publication on the stylistic matters on the EMA website.

Following this, the IE and MT QRD members agreed that both units of measurement are applicable in the EN version of the product information annexes and that the document of the stylistic matters will reflect these changes in due time. Therefore, this point 5.1.1 is also resolved.

The only outstanding issue is in the context of the clinical evaluation and implementation of appropriate wording (dosing regime/interval, inclusion of studies performed, etc.) into the product information, please see clinical assessment for further details.

6.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

In accordance with Articles 59(3) and 61(1) of Directive 2001/83 and with EMA Guidance (Operational procedure on Handling of "Consultation with target patient groups" on Package Leaflets (PL) for Centrally Authorised Products for Human Use), consultation with the target patient groups regarding the readability of the Package Leaflet (PL) for Ilaris was conducted as part of:

- Original Marketing Authorisation Application (MAA): Ilaris in Cryopyrin-Associated Periodic Syndrome (CAPS). The results of the readability testing demonstrated that the Patient Information Leaflet (PIL) is written in clear and user-friendly language, meeting the European Commission's Readability Guideline and were submitted in May 2009.
- New indication: Ilaris in Gouty arthritis. The results of the readability testing were submitted in July 2011.
- Line Extension for a new pharmaceutical form: Ilaris 150 mg powder and solvent for solution for injection (injection kit). Results of this focused consultation - covering the "instruction for Use" section of the PIL - were submitted in May 2011.
- New indication: Ilaris in Systemic Juvenile Idiopathic Arthritis (SJIA). The results of the readability testing were submitted in May 2013.
- Line Extension for a new pharmaceutical form grouped with type II variation for three new indications: Ilaris 150 mg/ml solution for injection and Tumour necrosis factor receptor associated periodic syndrome (TRAPS), Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), and Familial Mediterranean fever (FMF). The results of the readability testing were submitted in October 2016.

In this Type II variation, the company Novartis submitted an extension of indication for the treatment of Schnitzler's syndrome. In order to reflect this indication, the PL has been updated accordingly. No significant changes are made to the PL and the key information remain the same as the currently approved PL. The information proposed in the PL maintains the currently approved layout and format. The proposed changes are limited to the following:

Section 1 'What Ilaris is and what is it used for' includes addition of the Schnitzler's syndrome indication and a description in a patient friendly language.

Section 2 'What you need to know before you use Ilaris' includes addition of Schnitzler's syndrome to the statement 'Ilaris is not recommended for children or adolescents under 18 years of age.'

Section 3 'How to use Ilaris' includes instructions for the recommended dose, the highest dose a patient will receive, self-injection, how long to use and what to do if a patient forgets to inject a dose of Ilaris for the treatment of Schnitzler's syndrome.

Taking the above aspects into consideration, the applicant considers the results of the existing consultations with the target patient population are still valid, and therefore a full user testing or a focus test is not necessary, which is endorsed by the assessor.

6.1.2. Additional monitoring

N/A

6.1.3. Quick Response (QR) code

The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here).

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

Schnitzler syndrome (SchS) is a rare, chronic, systemic auto inflammatory with an onset in adults in their fifth decade of life. According to Orphanet (www.orpha.net), the portal for rare diseases and orphan drugs, SchS (Orpha number: ORPHA:37748) is listed as a rare disease but the exact prevalence is unknown (<1 per 1,000,000).

The first clinical signs of SchS are generally urticarial rash, mainly associated with recurrent fever or joint and/or bone pain. Skin symptoms are recurrent urticarial rashes presenting in all patients diagnosed with SchS, primarily affecting the trunk and the extremities. Elementary lesions consist of wheals, rose or red macules or gently raised papules or plaques, which resolve within 24 hours. The frequency and duration of the flares is variable and can be exacerbated by stress, infections, cold temperatures (i.e., during winter) or physical exercise. Skin biopsies have confirmed that the most typical skin finding is a neutrophilic urticarial dermatosis without vasculitis or dermal oedema. Another clinical sign is recurrent fever where body temperature can rise above 40°C.

Diagnosis of SchS is important to recognize due to its association with malignancy, which can impact the overall prognosis. The risk of developing lymphoproliferative disorders such as lymphoma, IgM myeloma or Waldenström's macroglobulinaemia is approximately 15-20% for patients with SchS, similar to that of patients who have monoclonal IgM gammopathy of unknown significance.

7.1.2. Available therapies and unmet medical need

There are currently no approved treatments for SchS. However, the most effective treatment for SchS to date is IL-1 inhibition with the majority of patients responding well to anakinra, an IL-1 receptor antagonist or canakinumab.

7.1.3. Main clinical studies

Due to the rarity of SchS worldwide, only one randomized, placebo-controlled trial in patients with Schnitzler Syndrome has been conducted by the applicant.

Study DDE03T was a Phase 2, multicentre, randomized, double-blind, placebo-controlled, investigator initiated trial (IIT) that evaluated safety and efficacy of canakinumab in SchS patients. The study was conducted in 4 centres in Germany. The study consisted of 4 Parts (A, B, C and D). Part A was a 7-day double-blind, placebo-controlled study of a single SC dose of canakinumab 150 mg. Part B was a 16-week open-label follow-up phase to establish the optimal dose of canakinumab (150 mg or 300 mg). Parts C (1 year) and D (3 years) comprised a 4-year open-label extension to evaluate long-term efficacy, quality of life, and safety.

The applicant also submitted a review of the scientific literature of canakinumab, anakinra and rilonacept used in SchS. The described small studies, analyses and case reports indicate the effectiveness of anti-IL-1 treatment in controlling signs and symptoms of SchS with the majority of patients achieving complete clinical response. However, due to rarity of the disease the number of the patients was low (n=25) and the data are limited.

Main clinical study from safety data set

SchS data:	CACZ885DDE03T (ILESCH), randomized, double-blind, placebo-controlled, phase II trial, of canakinumab in patients with SchS. (referred as **DDE03T**)

Supportive Data from the safety data set

AOSD data:	CACZ885GDE01T (CONSIDER), randomized, double-blind, placebo-controlled, phase II trial, of canakinumab in patients with AOSD (referred as **GDE01T**)
Pooled CAPS data:	meta-analysis including safety data from clinical trials CACZ885A2102, CACZ885D2201, CACZ885D2304, CACZ885D2306 and CACZ885D2308 of canakinumab in patients with CAPS.
pMI data:	CACZ885M2301 (CANTOS), randomized, double-blind, placebo-controlled phase III trial, of canakinumab in patients with post-myocardial infarction (referred as **M2301**)

7.2. Favourable effects

Study DDE03T met its primary endpoint. The results show a higher proportion of patients with complete clinical response in the canakinumab-treated group with 71.4% (n=5/7) compared to 0% in the placebo group (n=0/13) at Day 7 (p=0.001). Additionally a decrease in disease activity (PGA) was observed from baseline in the canakinumab-treated group (p=0.018). The difference in median changes in PGA total scores was canakinumab group -11 vs. placebo group 0 with p<0.0001.

Clinical improvement of symptoms as assessed by PGA were maintained even if the values varied due to the fact that the canakinumab administrations in the open label parts B and C were upon confirmed relapse. In part D canakinumab was given as needed based on previous responses in Part C (individual mean dosing intervals). Relapse of symptoms was not required for canakinumab dosing during part D.

7.3. Uncertainties and limitations about favourable effects

The number of patients enrolled in Study DDE03T was small (n=20). Only 15 patients completed the study.

Additionally the randomization in Part A (double-blind, placebo controlled phase) was unbalanced with only 7 patients being randomized to the canakinumab group. The submitted information regarding randomization and study drug distribution is insufficient. (MO)

The assessment of efficacy of canakinumab is compromised due to insufficient documentation and the unclear circumstances around randomisation and how this impacts the results. Further clarifications presented by the MAH with the Response to the Request for Supplementary Information are considered insufficient.

The main issues whether the study has been conducted such that the results can be considered accurate and reliable, and whether the level and quality of the documentation provided in the dossier can be considered fit for purpose for a regulatory submission are not resolved and do still remain. The details provided in the documents do not provide a sufficient basis for an adequate assessment, and the tables and figures reproduced in the AR (that would also be reproduced in an EPAR in due course), the underlying statistical methods and their appropriateness cannot be ascertained.

The irregularities in the randomisation process raise substantial concerns regarding the validity of the statistical analyses as presented in documentation submitted by the MAH. Furthermore, the overall GCP compliance of the study as already questioned in the 1st RSI and the responses provided by the MAH do not overall mitigate these previously stated concerns.

7.4. Unfavourable effects

The safety profile has been established for canakinumab in several other indications. There is an increased risk for infection for patients treated with canakinumab. This risk is already known and is addressed in the SmPC and the RMP. Also known is the risk for severe opportunistic infections. In Study DDE03T one case of sepsis with a fatal outcome occurred. Questions on this case are currently not resolved. PK data were not evaluated therefore no data on the exposure are available.

7.5. Uncertainties and limitations about unfavourable effects

Uncertainties concerning the provided safety profile:

The number of SchS within the safety data set is limited (n=20) due to the strong rarity of the disease. A large number of data comes from supportive safety of patients with post-myocardial infarction and to a lower extend from patients with CAPS and AOSD showing a similar age or clinical symptoms, respectively, as compared to SchS. However, the acquired safety data may not be completely transferable to SchS due to disease-specific unique pathomechanisms.

Additionally the recommended dosing regimen according to the SmPC with dosing Q8W was not evaluated in Study DDE03T. In the open label extension Phase (>4 years) patients were dosed based upon relapse of symptoms. 17.6% of the patients were without a relapse and thus without administration of canakinumab for over 12 months. Therefore, it is unclear whether the safety results in these patients would be similar with the Q8W dosing regimen.

7.6. Effects Table

Table 9 Effects Table for Ilaris in patients with Schnitzler Syndrome

Effect	Short description	Unit	CANA (50)*/ 150/ 300 mg	PCB	Uncertainties / Strength of evidence	References
Favourable Effects						
CR	Proportion of patients with complete clinical response	%	71,4	0	Only 20 patients, unbalanced randomized /Primary Endpoint at day 7 (p=0.001)	**CSR DDE03T**
PGA	Change in PGA score from baseline (median)	P	-11	0	Only 20 patients, unbalanced randomized/ Secondary Endpoint at day 7 (p<0.0001)	**CSR DDE03T**
Unfavourable Effects						
TEAEs	SOC Infections and Infestations	%	100	/	4 year extension phase with 17 patients, majority within respiratory tract, mild and resolved.	**Study DDE03T**
		%	51.5	50.4	Large patient population (6178 treated; 3348 placebo) with similar age as compared to SchS	Study M2301
	Nasopharyngitis	%	64.7	/	4 year extension phase with 17 patients, no placebo control	**Study DDE03T**
SAE	fatal sepsis	%	10	/	1/20 of SchS patients initially included in the trial. Relation to CANA treatment is suspected based on mode of action.	**Study DDE03T**
		%	0,17	0,13	Large patient population (6178 treated; 3348 placebo) with similar age as compared to SchS but other comorbidities	Study M2301

Abbreviations: CANA, canakinumab; CR, clinical response; PCB, placebo; PGA, physician global assessment; SOC, system organ class; TEAE, treatment emergent adverse event

Notes:*additional dosing of 50mg was used in study M2301

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

There is an unmet medical need for the treatment of patients with Schnitzler syndrome (SchS). SchS is associated with malignancy. The risk of developing lymphoproliferative disorders such as lymphoma,

IgM myeloma or Waldenström's macroglobulinaemia is approximately 15-20% for patients with SchS, similar to that of patients who have monoclonal IgM gammopathy of unknown significance.

The results from Study DDE03T indicate efficacy of canakinumab in this patient population with 71.4% of patients having complete response 7 days after the first administration and inflammatory markers (i.e. CRP and SAA) decreased to normal ranges in the majority of patients. Long-term data (>4 years) indicate that the improvement in clinical symptoms is maintained.

However, the results cannot be considered accurate and reliable due to apparent errors in the randomization processes and incomplete documentations. Hence, the true efficacy of canakinumab is not known.

The safety profile of canakinumab is well established in other indications and appears similar in patients with SchS. Treatment emergent AEs by SOC in SchS patients mostly consisted of infections and Infestations and Musculoskeletal and connective tissue disorders. The rate of AEs and SAEs were similar to the already established safety profile of canakinumab and manageable. One patient died during the study due to sepsis. Infections and opportunistic infections are known risks that has been addressed in the RMP and SmPC.

However, it is unclear whether the safety results and therewith the B/R ratio in these patients would be similar with the proposed Q8W dosing regimen.

7.7.2. Balance of benefits and risks

The results show efficacy in reducing signs and symptoms in patients with Schnitzler Syndrome. The safety results from Study DDE03T were similar to the known safety profile of canakinumab. However, the number of patients was very limited (n=20) making the results hard to interpret. Due to the substantial uncertainties regarding the study conduct, documentation and reporting, the quality basis of the main study, the proposed posology, the randomization of study DDE03T and consequently the impact of these significant issues on the results several Major Objections and Other Concerns have been raised that are currently not resolved. Therefore, the Benefit/ Risk Balance is negative at the moment.

7.7.3. Additional considerations on the benefit-risk balance

7.8. Conclusions

The overall B/R of Ilaris for the treatment of patients with Schnitzler syndrome is currently negative.