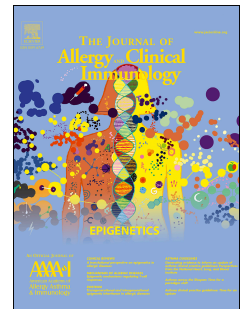


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Long-term Efficacy of Canakinumab in the Treatment of Schnitzler Syndrome

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Title page

Long-term Efficacy of Canakinumab in the Treatment of Schnitzler Syndrome

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Conflict of interest statement: K. Krause has received grants from Novartis and Roche, and payment for lectures and/or consultancies from Novartis, Roche and SOBI outside the submitted work. N. Wagner has received a grant and payment for lectures and consultancies from Novartis outside the submitted work. M. Maurer has received institutional funding for research and honoraria for consulting and lectures from Novartis outside the submitted work. H. Bonnekoh, A. Ellrich, A. Tsianakas and J. Fischer have no conflicts of interest to declare.

Capsule Summary: This 4-year long-term study confirms that canakinumab treatment effectively reduces the clinical signs and symptoms of Schnitzler syndrome, decreases inflammatory markers, and improves overall quality of life. However, canakinumab therapy requires close monitoring for infections.

Keywords: Schnitzler syndrome, canakinumab, interleukin-1, autoinflammation, urticaria

Letter to the Editor (1,851 words)

To the Editor:

Schnitzler syndrome (SchS), a rare inflammatory disorder characterized by chronic urticarial rash, bone and joint inflammation and recurrent fever, has only around 300 reported cases worldwide.¹ Aberrant NLRP3 inflammasome signaling and cytokine pathway dysregulation play a crucial role in SchS pathophysiology,² along with elevated levels of pro-inflammatory interleukin-1 β (IL-1 β).³ Systemic symptoms can severely impact quality of life (QoL) but no approved treatment for SchS exists; due to its rarity, therapeutic evidence comes mainly from small case reports and case series, rather than controlled trials. Thus, SchS patients urgently require effective new therapies.

Good clinical responses have been achieved with the IL-1 blockers, anakinra⁴ and rilonacept.⁵ Canakinumab, a monoclonal antibody targeting IL-1 β , is approved for the treatment of cryopyrin-associated periodic syndrome (CAPS) and Still's disease; both conditions share similar clinical features with SchS. Previously, we reported efficacy of canakinumab in SchS from a 4-month randomized placebo-controlled trial involving 20 patients.⁶ Herein we report results from the 4-year extension phase of this trial (ClinicalTrials.gov identifier: NCT01390350; EudraCT no. 2010-024156-28).

In this investigator-initiated phase II study, canakinumab-responding patients who completed Parts A (0–7 days) and B (16 weeks) entered the open-label extension phase to monitor long-term efficacy, QoL and safety. During part C of the study (one year), patients were either taking canakinumab 150mg or 300mg based on previous individual responses in parts A and B. Patients who were initially assessed as complete clinical responders to canakinumab 150mg in parts A/B (no or minimal disease activity in PGA scores within 7 days of the first injection) and normalized CRP, continued with this dose when needed (upon confirmed relapse of symptoms) in part C. Patients with initial partial clinical response to canakinumab 150mg (mild to moderate disease activity in PGA scores within 7 days of the first injection) with or without CRP above the reference level ($\geq 0.5\text{mg/dl}$) were administered

canakinumab 300mg when needed (upon confirmed relapse of symptoms) in part C. Confirmed relapse of symptoms was defined as $\geq 50\%$ increase in the total PGA score as compared to the total PGA score 7 to 14 days after canakinumab initiation. In part D (three 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 (**Figure 1**). Outcomes were measured in all patients who received canakinumab treatment, and the results were assessed vs. baseline levels (using Wilcoxon matched-pairs signed rank test). Long-term efficacy was evaluated using total physician global assessment (PGA) scores (grading 0–20 of five key SchS symptoms: urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain)⁶ on a 5-point Likert scale, and single sub scores (grading 0–4). Serum level changes in the inflammatory markers C-reactive protein (CRP) and serum amyloid A (SAA) were measured. Also, health-related QoL was assessed using the Dermatology Life Quality Index (DLQI), a skin disease-specific QoL questionnaire, and a generic health-related QoL instrument, the 36-item short form health survey (SF-36), both with recall periods of one week.

Adverse events (AEs; MedDRA terminology) and routine safety laboratory assessments were recorded, and physicians performed physical examinations and electrocardiograms. Spearman's rank correlation coefficient was used to analyze individual dosing intervals with mean disease activity, inflammatory markers and QoL.

Seventeen patients (female/male=8/9; median age 64 years; range 51–76 years) entered the open-label extension study from July 2012–February 2013; 15 completed the full four years. The long-term clinical efficacy of canakinumab was high with most patients experiencing no/minimal/mild disease activity, demonstrated by significantly lower total PGA scores at all visits from six months (PGA of 9) to 57 months (PGA of 4) vs. baseline scores (PGA of 14.5; $P=0.0063$ – 0.0005 ; **Figure 2A, Table E1**). Individual reductions in total PGA scores over time are shown in **Figure E1**. Patients achieved significant improvements vs. baseline scores in

specific SchS symptoms (urticarial rash, fatigue, and arthralgia/bone pain) after six months of canakinumab treatment. Fever and myalgia had significantly improved by 36 months (**Table E1**). During Part D, where patients injected canakinumab as needed, clinical efficacy was highest.

The number of complete clinical responders at 6, 12, 36 and 57 months were two, three, five and six, respectively. No patient experienced a substantial loss of efficacy over time; one patient escalated the dosage from 150mg to 300mg canakinumab at the end of the second study year (part D) because of increased musculoskeletal complaints as assessed by PGA sub scores myalgia and arthralgia/bone pain (3-4 of a max. of 4) at subsequent visits during months 12-24. Symptom relapse was rare, occurring mainly after treatment interruption or infection. Clinical responses mirrored significant decreases and normalization in CRP, which was stable throughout the study ($P=0.04-0.0001$); median baseline CRP level (6.09mg/dL) decreased by six months (1.02mg/dL), remaining within the reference level (≤ 0.5 mg/dL) at most visits (**Figure 2B**). In five patients, CRP levels reduced but remained above reference values. Two of these patients displayed suboptimal clinical responses and discontinued the study due to serious AEs (sepsis with a fatal outcome and multiple myeloma). SAA levels significantly decreased from baseline (180mg/L) throughout the study (15.8mg/L at six months and 11.1mg/L at 57 months: $P=0.03-0.0005$ **Figure 2C**). Median paraprotein levels changed from 566mg/dL at baseline to 866mg/dL at month 57. In nine patients (eight with IgM κ , one with IgG κ) out of 11 for whom complete data were available, paraproteins increased slightly, in two patients with IgM κ , immunoglobulins decreased.

Patient's QoL significantly improved throughout the study; a median baseline DLQI score of nine (moderate QoL impairment) reduced to one (no QoL impairment) after six months of canakinumab treatment and remained low throughout the study ($P=0.01-0.0005$; **Figure 2D**). The median SF-36 physical component significantly increased; 28.3 at baseline to 43.9 at six months and 43.2 by 57 months ($P=0.03-0.002$; **Figure 2E**). In contrast, SF-36 mental component scores were barely affected (**Figure 2F**).

Based on their responses to the previous 4-month treatment, eight patients received canakinumab 150mg, and nine patients received canakinumab 300mg (**Figure E2**). Median dosing intervals were 62 days and 63 days for canakinumab 150mg (n=8) and 300mg (n=9), respectively. Dosing intervals were associated with scores of PGA and SF-36 physical domains; a lower disease activity (measured by total and individual PGA scores) allowed for prolonged dosing intervals (measured by injection intervals in days: total PGA, $r=-0.7549$, $P=0.0007$; myalgia, $r=-0.7627$, $P=0.0006$; arthralgia/bone pain, $r=-0.7264$, $P=0.0013$; fatigue, $r=-0.5212$, $P=0.03$). Longer canakinumab injection intervals also correlated with improved SF36 physical component scores ($r=0.5319$, $P=0.03$).

In total, 176 AEs occurred, 169 of which were mild or moderate. Respiratory tract infections (n=42 in 14 patients) and urinary tract infections (n=12 in five patients) were most common. Seven serious AEs occurred, including a case of multiple myeloma (patient withdrew from the study) (**Table E2**). Two suspected unexpected serious adverse reactions (SUSARs) occurred. In one case of sepsis a causative relationship with canakinumab was suspected. This 72-year-old patient with comorbid heart failure who was on concomitant therapy with prednisone developed sinusitis with fever and anemia after eight months of canakinumab 300mg and shortened dosing intervals from 56 to 28 days due to increased disease activity. Despite extensive diagnostic and therapeutic measures, he died 10 weeks later because of sepsis with atypical mycobacteriosis. A second 68-year-old patient experienced pneumonia with transient hemiplegia. Canakinumab treatment was paused and restarted after complete recovery. In this case, a causative relationship with canakinumab was considered possible.

Here we report the first long-term, multi-center study to investigate the treatment of canakinumab in patients with SchS. The majority of patients in this study experienced no/minimal/mild disease activity during their treatment, reflected by significant improvements in PGA scores over time, and normalized levels of CRP and SAA inflammatory markers.

We used PGA scores to assess the key symptoms of SchS. Patients achieved significant improvements vs. baseline scores in most symptoms after six months of canakinumab

treatment. Fever and myalgia took longer to improve (36 months), likely due to the intermittent nature of fever and its median baseline score of 0. These two symptoms were the first to return when the effects of canakinumab dissipated.

Higher disease activity and inflammatory markers at months 6 and 12 as compared to months 36–57 are explained by the study design, which required relapse of clinical symptoms for canakinumab treatment during the first year (part C). The median dosing interval of 62 to 63 days is comparable to the 8-week dosing regimen used for CAPS. As in our study, canakinumab dosing intervals in CAPS patients are adjusted depending on clinical severity.⁷ de Koning *et al*⁸ used a different dosing interval of 150mg canakinumab every four weeks over nine months in eight SchS patients; although most patients experienced good clinical and laboratory responses, the 150mg dose was insufficient to control symptoms in one individual. Considerable inter-individual heterogeneity has been observed in the time to relapse after canakinumab administration, ranging from 40 to 234 days (median 72 days) after the last canakinumab injection.⁸ Here, we demonstrate a broad range in dosing intervals from 28 days to ≥ 1 year (three patients on canakinumab 150mg were symptom-free for ≥ 12 months). The time to relapse inversely correlates with disease activity, in line with CAPS observations whereby more severely affected patients require more frequent dosing.⁷ SchS patients with less severe disease may have lower IL-1 β levels; thus, IL-1 β downregulation and clinical remission induced by canakinumab may last longer. Based on our results, we recommend a dosing regimen of 150mg canakinumab every eight weeks. If clinical response is unsatisfactory after 7–14 days, an additional 150mg can be administered, with a 300mg maintenance dose every eight weeks. Injection intervals can be individualized in complete responders.

The age group of our SchS study (median 64 years) was similar to that in the CANTOS study (mean 61.1 years), which included >10,000 patients with previous myocardial infarction treated with long-term canakinumab.⁹ In our study, 176 AEs occurred, 169 of which were mild or moderate. In line with the elderly population in CANTOS, respiratory tract infections

were most common. However, respiratory infections are prevalent in the general population, especially when considered over four years. IL-1 blockade can interfere with patients' immune responses to bacteria, increasing the risk of opportunistic infections, which could explain the two SUSARs. During a long-term multicenter study with the IL-1 receptor antagonist anakinra in SchS, two fatal infections were reported.⁴ Thus, it is essential to monitor, vaccinate and screen patients appropriately to mitigate the risk of complications. Despite a considerable number of infections during our study, AE frequencies did not differ between 300mg and 150mg canakinumab doses.

SchS is rare; thus, recruiting large patient numbers is challenging. This study is limited by low patient numbers, making significance levels difficult to establish. Some patients missed visits, compounding already small quantities and potentially impacting the robustness of data. Further, more extensive studies are required to extend and confirm our observations.

In conclusion, this first long-term, multi-center study confirms that canakinumab treatment effectively reduces the clinical signs and symptoms of SchS, decreases inflammatory markers, and improves overall QoL, with sustained effects over four years.

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Figure legends

Figure 1. Patient disposition showing the number of patients screened, randomized, and those who completed Parts A to D of this 4-year study. Results from Parts A and B (text in light grey) have previously been published.⁶

Figure 2. PGA total scores (A), CRP (B), SAA (C), DLQI (D), SF-36 physical component score (E) and mental component score (F) from baseline to 57 months in SchS patients treated with canakinumab 150mg or 300mg. Significance assessed by Wilcoxon matched-pairs signed rank test. Asterisks indicate significant differences (* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$) vs. baseline. Data are shown as interquartile ranges for all visits. Grey-shaded areas reflect study parts A and B.

CRP, C-reactive protein levels; DLQI, dermatology life quality index; PGA, physician global assessment; SAA, serum amyloid A levels; SchS, Schnitzler syndrome; SF-36, 36-item short form health survey.

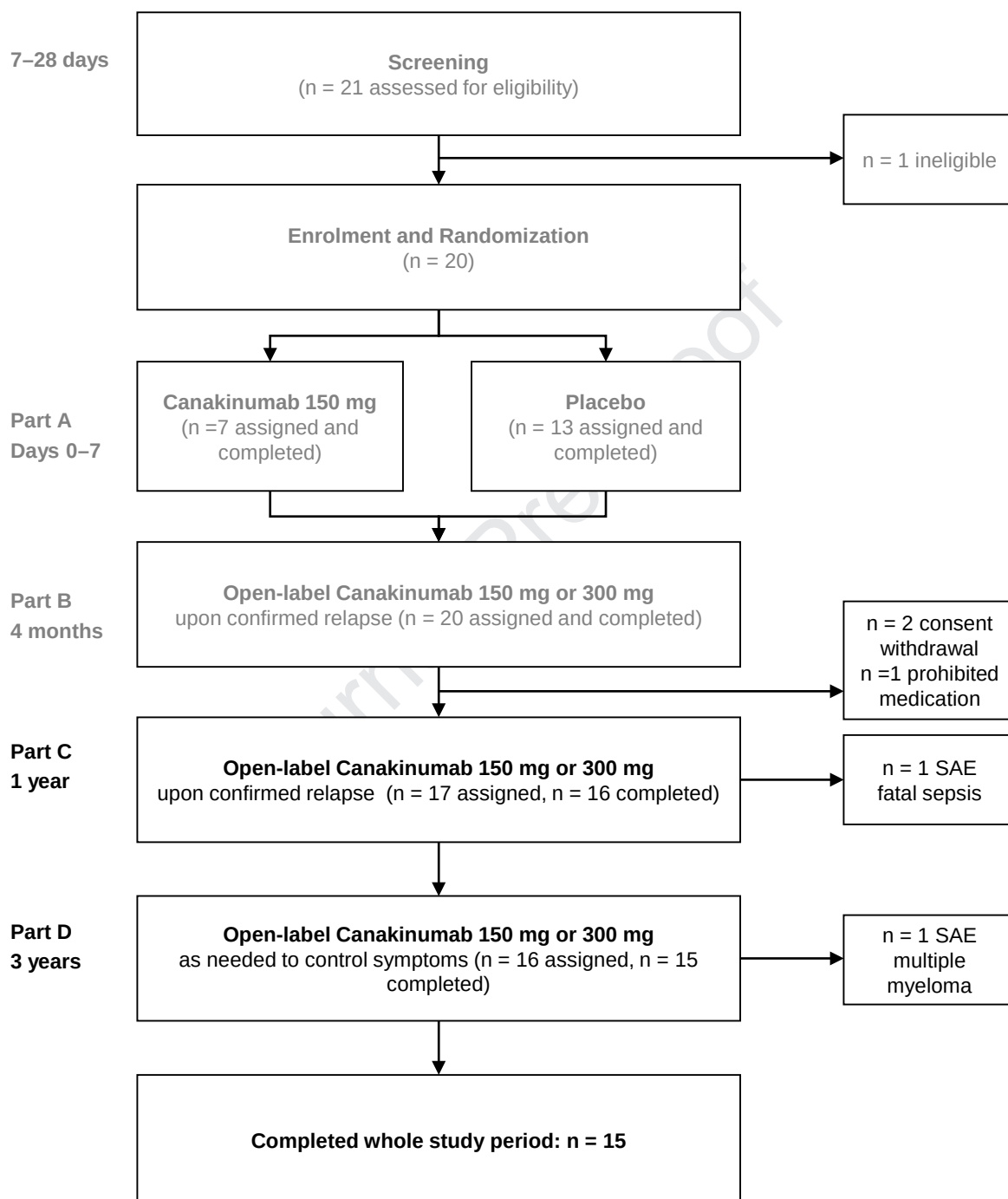
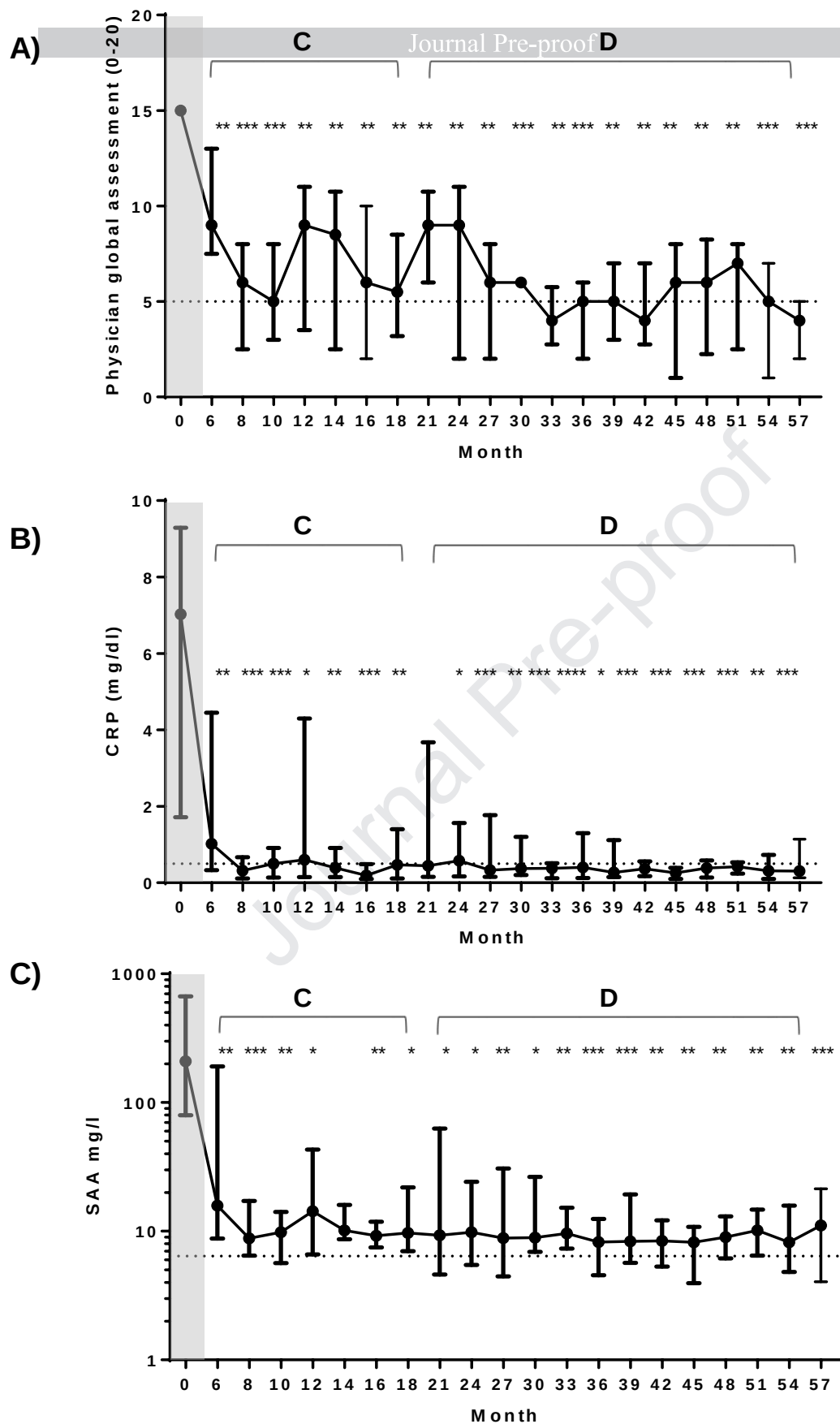


Figure 1



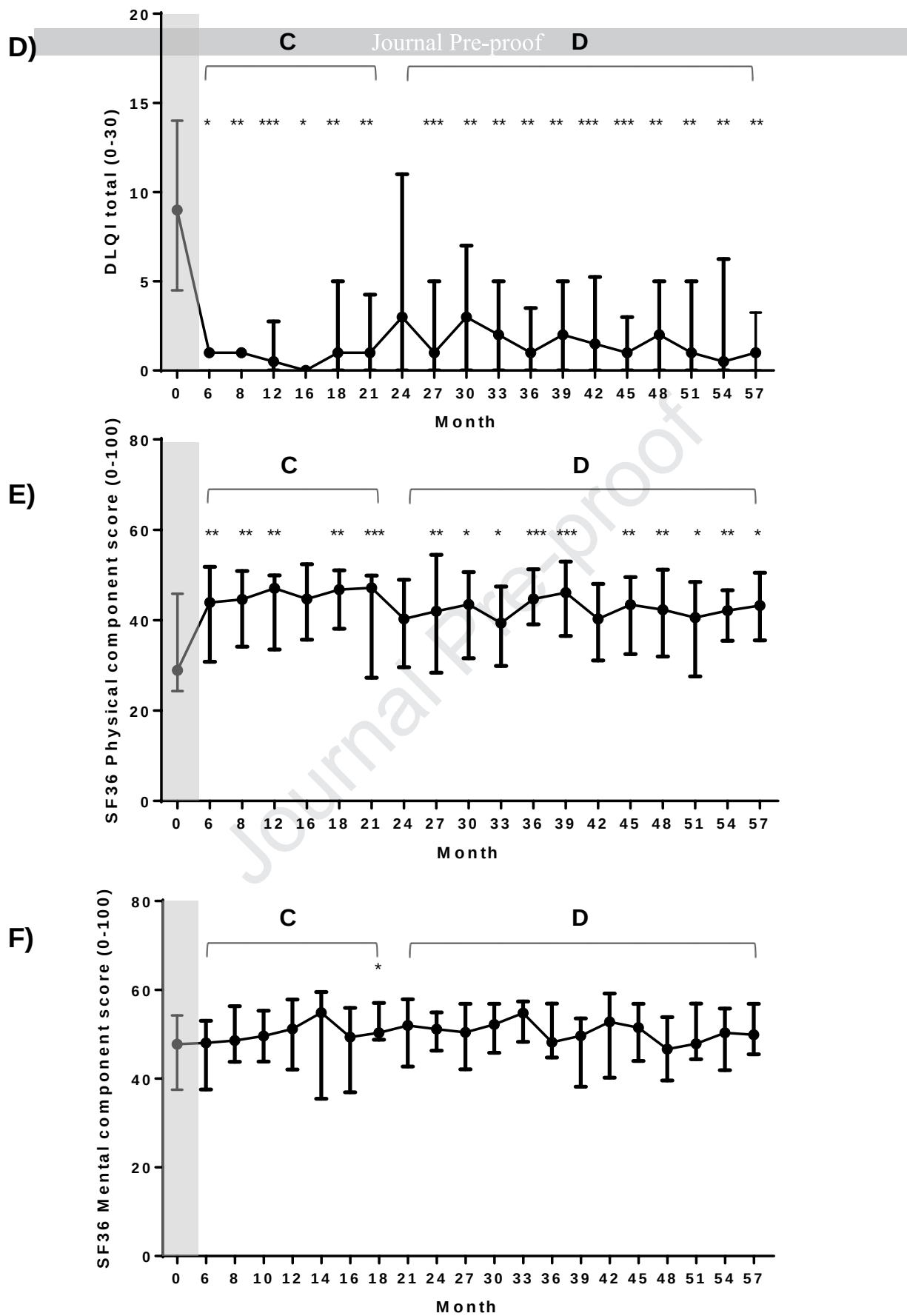
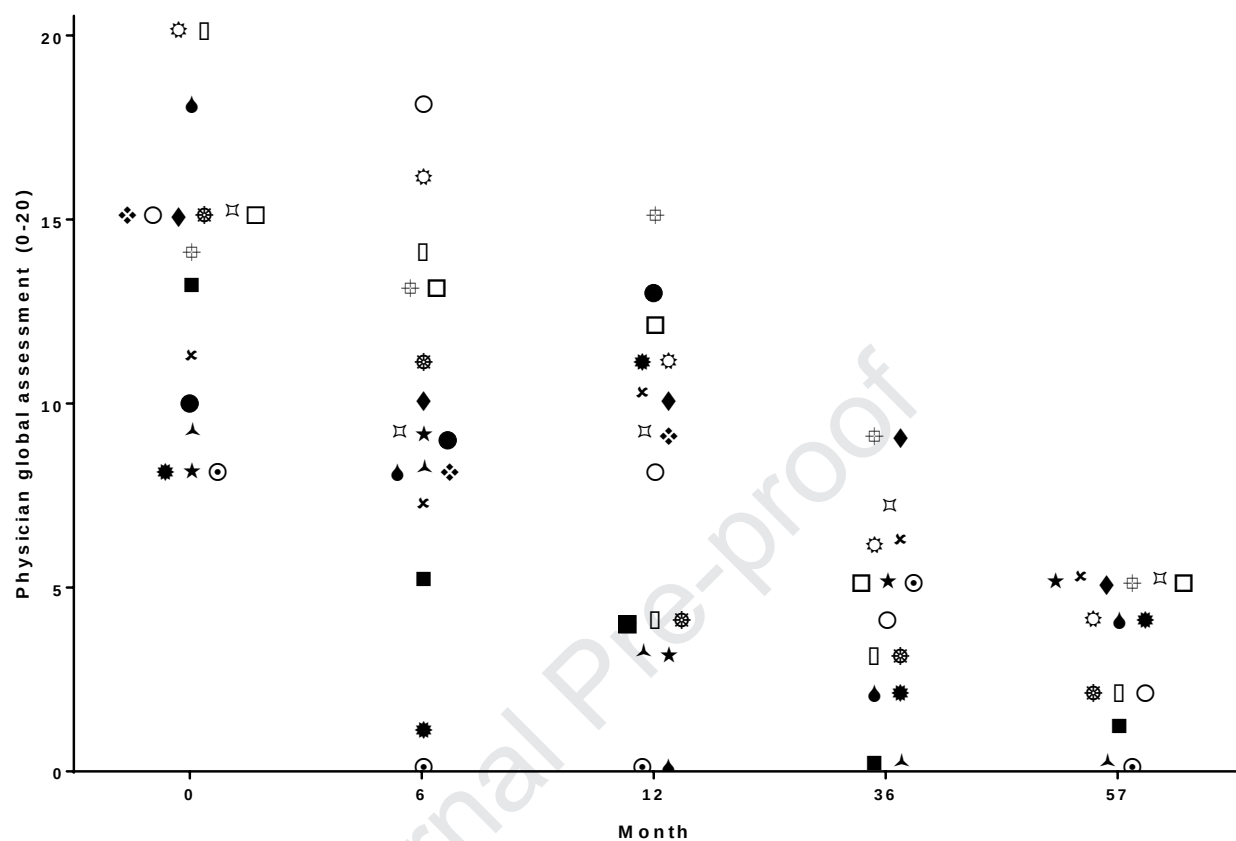


Figure 2



Patient number and symbol:

1	⊗	10	□
2	⊙	11	★
3	▲	12	◆
4	⊗	13	⊗
5	⊕	14	×
6	●	15	□
7	○	16	⌘
8	⊕	17	●
9	■		

Figure E1

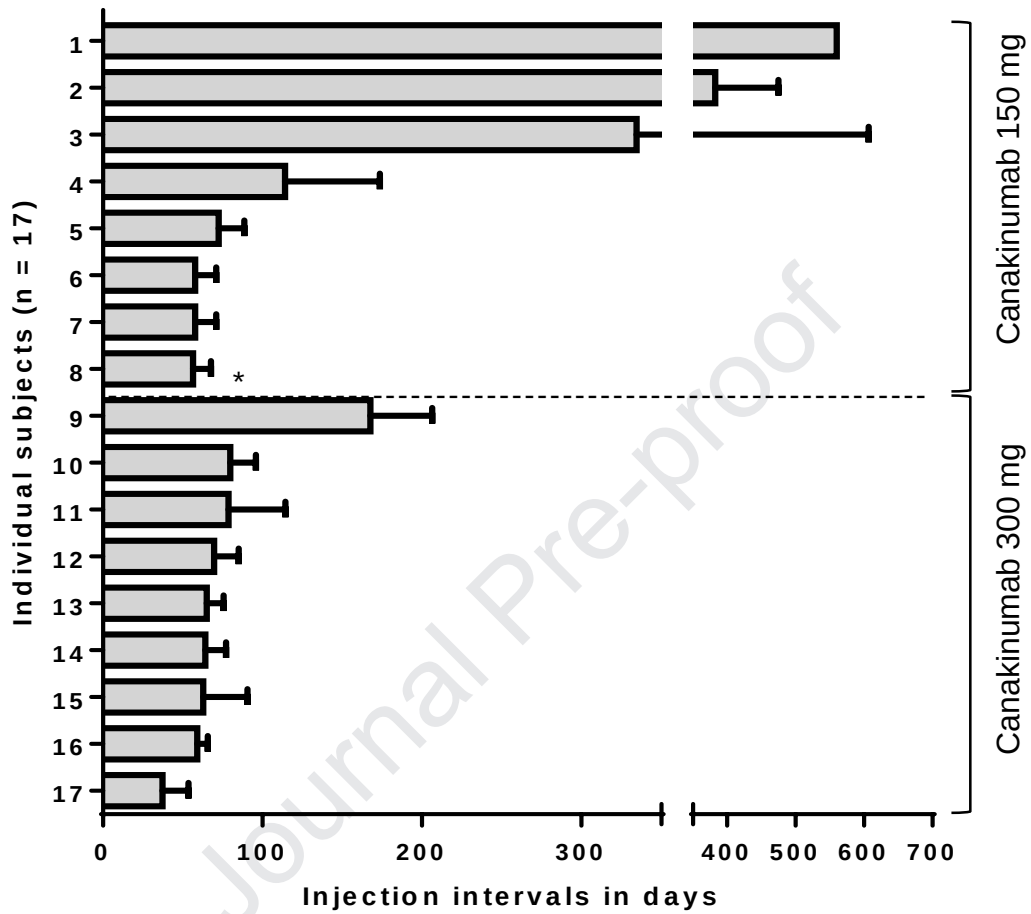


Figure E2

Online Repository

Long-term Efficacy of Canakinumab in the Treatment of Schnitzler Syndrome

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Table E1: Physician's Global Assessment total and sub scores during the study

Physician global assessment	Baseline (Part A)	Month 6 (Part C)		Month 12 (Part C)		Month 36 (Part D)		Month 57 (Part D)	
	Median (range)	Median (range)	P*	Median (range)	P*	Median (range)	P*	Median (range)	P*
Total (0-20)	14.5 (8-20)	9 (1-18)	0.0014	9 (0-15)	0.0016	5 (0-9)	0.0007	4 (0-5)	0.0007
Urticarial rash (0-4)	4 (0-4)	2 (0-4)	0.0122	1 (0-4)	0.0034	0 (0-3)	0.0006	0 (0-2)	0.0007
Fatigue (0-4)	3 (0-4)	2 (0-4)	0.0033	3 (0-4)	0.008	1 (0-3)	0.0032	1 (0-2)	0.0009
Fever (0-4)	0 (0-4)	0 (0-3)	0.276	0 (0-3)	0.1779	0 (0)	0.0218	0 (0)	0.0218
Myalgia (0-4)	3 (0-4)	2 (0-4)	0.2792	2 (0-4)	0.1209	1 (0-3)	0.0058	1 (0-2)	0.0024
Arthralgia/ bone pain (0-4)	3.5 (1-4)	3 (0-4)	0.0046	2 (0-3)	0.0025	1 (0-3)	0.0022	1 (0-3)	0.0019

*compared with Baseline

Table E2: Characteristics of adverse events >n=1 and serious adverse events

	n (patients)	No. of events	
	17		
At least one adverse event (AE)	17	176	
Cardiovascular:			
Hypertension	4	6	
Dysrhythmia	4	5	
Gastrointestinal:			
Gastrointestinal infection	3	5	
Epigastric pain	3	3	
Elevated liver enzymes	2	2	
Colon adenoma	1	2	
Diarrhea	2	2	
Musculoskeletal and connective tissue:			
Lumbago	3	3	
Arthrosis/arthritis	5	6	
Joint or bone pain	3	4	
Muscular pain/cramps	3	3	
Spinal disc herniation	2	2	
Respiratory:			
Respiratory tract infection	14	42	
Eye, Ear, nose, throat:			
Conjunctivitis	2	2	
Tinnitus	2	2	
Sinusitis	1	2	
Urogenital:			
Urinary tract infections	5	12	
Prostate hyperplasia	2	2	
Biopsy of the prostate	1	2	
Skin:			
Eczema	4	5	
Skin carcinoma	2	2	
Atypical nevus (excision)	2	2	
Tinea	2	2	
Oral:			
Dental root inflammation	2	2	
Gingivitis	1	2	
Other:			
Night sweating	2	2	
Vertigo	2	3	
Serious adverse event (SAE)			
At least one SAE	6	7	
	Relationship with study drug	No. of events	Canakinumab dose (mg)
Pneumonia with consecutive paraplegia; recovered	Suspected	1	150
Sepsis due to atypical mycobacteriosis; a fatal outcome	Suspected	1	300
Worsening of inguinal hernia; recovered	Not suspected	1	150
Multiple myeloma; left the study	Not suspected	1	150
Choledocholithiasis; recovered	Not suspected	1	300
Leiomyoma; recovered	Not suspected	1	300
Craniocerebral trauma due to assault; recovered	Not suspected	1	150

Figure legends

Figure E1. Individual total physician global assessment (PGA) scores of 17 Schnitzler syndrome patients over the 4-year study period.

Figure E2. Individual dosing regimens of 17 Schnitzler syndrome patients receiving either 150mg or 300mg canakinumab treatment during the open-label extension. Bars indicate the mean number of days between treatment injections. *Patient was switched from canakinumab 150mg to 300mg in the second study year because of increased musculoskeletal complaints.