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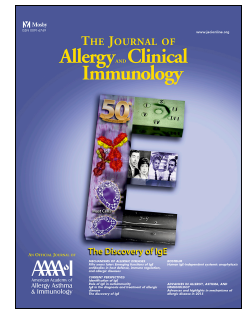
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**Efficacy and safety of canakinumab in Schnitzler's syndrome: a multi-center
randomized placebo-controlled study**

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Abstract

Background: Schnitzler's syndrome is an adult-onset autoinflammatory disease characterized by urticarial exanthema and monoclonal gammopathy accompanied by systemic symptoms such as fever, bone and muscle pain. Up to now, approved treatment options are not available.

Objective: We here assessed the effects of the anti-IL-1 β monoclonal antibody canakinumab on the clinical signs and symptoms of Schnitzler's syndrome.

Methods: In this phase II, randomized placebo-controlled multi-center study, 20 patients with active disease enrolled in four German study centers. Patients were randomly assigned to receive single subcutaneous canakinumab 150 mg or placebo injections for 7 days, followed by a 16-week open-label phase with canakinumab injections upon confirmed relapse of symptoms. The primary endpoint was the proportion of patients with complete clinical response evaluated by physician global assessment at day 7. Key secondary endpoints included changes in patient-reported disease activity (Schnitzler activity score), inflammation markers (C-reactive protein [CRP], serum amyloid A [SAA]) and quality of life assessments (DLQI, SF-36).

Results: The proportion of patients with complete clinical response at day 7 was significantly higher ($P = 0.001$) in the canakinumab-treated group ($n = 5/7$) than the placebo group ($n = 0/13$). Levels of inflammation markers CRP and SAA and quality of life scores significantly reduced in canakinumab-treated but not in placebo-treated individuals. Positive effects continued up to 16 weeks. Adverse events were manageable and included respiratory tract infections, gastrointestinal symptoms and hypertension.

Conclusion: In this first placebo-controlled study, canakinumab was effective in patients with Schnitzler's syndrome, and thus canakinumab may be further evaluated as a therapeutic option for this rare disease.

Clinical implications: Currently, there is no approved treatment for Schnitzler's syndrome. Our study results implicate that continuous canakinumab treatment effectively controls the symptoms and the inflammation that underlies this disabling disease.

Capsule summary: This is the first randomized placebo-controlled study in Schnitzler's syndrome. All patients responded to canakinumab treatment, and most of them demonstrated complete symptom control.

Keywords: Autoinflammatory, Canakinumab, Interleukin-1, Schnitzler's syndrome, Urticaria

Word count: 3908

Abbreviations:

ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain

CAPS: Cryopyrin-associated periodic syndrome

CRP: C-reactive protein

DLQI: Dermatology life quality index

IL: Interleukin

IL-1Ra: Interleukin-1 receptor antagonist

PGA: Physician global assessment

SAA: Serum amyloid A

Introduction

Schnitzler's syndrome, first reported in 1972 by the French dermatologist Liliane Schnitzler,¹ is a multifactorial systemic inflammatory disorder with late onset, usually at around 50 years of age.³ It is characterized by chronic urticarial rash and monoclonal gammopathy (typically IgM, less often IgG).⁴ Symptoms frequently associated with Schnitzler's syndrome are recurrent fever attacks, bone and muscle pain, arthralgia and lymphadenopathy.⁵ Schnitzler's syndrome is ultra-rare with less than 300 cases reported in the literature.^{4, 6} However, it is likely that many cases presenting with therapy-refractory chronic urticarial eruptions are undiagnosed. Patients usually suffer from severe quality of life impairment and may develop malignant B-Cell lymphoma such as Waldenström's macroglobulinemia in around 15% of cases.⁷

Schnitzler's syndrome is held to be a paradigm of an acquired and late onset autoinflammatory disease, a group of diseases characterized by inflammasome activation and IL-1-driven morbidity and mortality. This notion is based on several independent lines of evidence. First, the clinical phenotype shares many similarities with cryopyrin-associated periodic syndrome (CAPS), a member of the monogenic systemic autoinflammatory disorder group. Second, Schnitzler's syndrome patients exhibit changes in the expression of inflammasome components that are typical for autoinflammatory disorders including apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the P2X7 receptor.⁸ Third, IL-1 β secretion from peripheral blood mononuclear cells of Schnitzler's syndrome patients is increased.⁹

Approved treatment options are completely lacking in Schnitzler's syndrome. The use of systemic corticosteroids, other immunosuppressives and non-steroidal antiphlogistics has demonstrated poor efficacy.⁴ Recently, anti-IL-1 targeting therapies, in case reports on anakinra treatment and two open-label studies with rilonacept and canakinumab, have been shown to be very effective in reducing the clinical symptoms and inflammation in Schnitzler's syndrome.⁹⁻¹³ Canakinumab is a fully human IL-1 β -specific monoclonal antibody approved for the treatment of CAPS,¹⁴ systemic juvenile idiopathic arthritis¹⁵ and therapy-refractory

110 gout.¹⁶ Here, we report the efficacy and safety of canakinumab in the first randomized,
111 double-blind, placebo-controlled study in patients with Schnitzler's syndrome.

Methods

Study design

This investigator-initiated study of canakinumab in 20 patients with active Schnitzler's syndrome was conducted in four German study centers and consisted of three parts, two of which have been completed. The first part was an initial 7-day double blind, placebo-controlled study of a single subcutaneous dose of canakinumab 150 mg. The second part was a 16-week open-label follow-up to establish the optimal dose of canakinumab, 150 or 300 mg, and to assess adverse responses. The third part, a 4-year open label extension to monitor long-term efficacy, quality of life and unwanted effects, is ongoing.

For part one of the study, after screening for 7 to 28 days, patients were assigned randomly (1:1) to receive a single subcutaneous injection of canakinumab 150 mg or placebo at day 0. No stratification was applied. Central block randomisation was used to form the allocation list for the two treatment groups. Patients, investigators and site personnel were blinded to the treatment assignment. To preserve blinding, canakinumab and placebo were visually indistinguishable and packaged identically. Changes in clinical symptoms, inflammation markers, quality of life and adverse events were assessed for the next 7 days. Following treatment response evaluation at day 7, patients were unblinded and moved to the open-label phase.

In the 16-week open-label follow-up phase of the study, all patients were treated with canakinumab injections depending upon relapse or worsening of symptoms. Patients with complete clinical response (as defined below) to canakinumab 150 mg and normalized C-reactive protein (CRP) levels continued with canakinumab 150 mg injections when needed. Partial responders to canakinumab 150 mg with or without CRP above the upper limit of normal (≥ 0.5 mg/dl) were given canakinumab 300 mg upon relapse/worsening of the disease. At all decision steps, non-responders left the study.

Patients

For inclusion, patients had to fulfil the diagnostic criteria established by Lipsker et al. in 2001. These consist of monoclonal gammopathy and chronic urticarial rash combined with at least two of the following symptoms: fatigue, recurrent fever, myalgia, arthralgia or arthritis, lymphadenopathy, hepato-/splenomegaly, leukocytosis and/or elevated erythrocyte sedimentation rate, and abnormal bone morphology.⁵ Only adult patients (≥ 18 years) with a physician global assessment (PGA) score of ≥ 8 (range 0 - 20) and CRP level above the upper limit of normal at visit 2 (day 0) were eligible to participate in the study. Further inclusion criteria were the willingness to complete all study visits and study-related procedures, a negative pregnancy test and effective contraceptive methods for women of childbearing potential. Exclusion criteria included active tuberculosis and other chronic infections, on-going treatment with IL-1 blockers, other biologics or immunosuppressives and the presence of malignancies within the last 5 years.

The study was approved by a central institutional review board and the ethics committee of each study center (EudraCT nr. 2010-024156-28) and followed Good Clinical Practice guidelines and the Declaration of Helsinki. The ClinicalTrials.gov identifier is NCT01390350. All patients gave written informed consent prior to any study-related procedures.

Assessments

The PGA was the primary instrument used to assess the efficacy of canakinumab treatment. For the PGA, the 5 key symptoms of Schnitzler's syndrome (urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain) were each graded on a 5-point Likert scale with 0 = no, 1 = minimal, 2 = mild, 3 = moderate and 4 = severe disease activity. The total PGA scores ranged between 0 and 20. Patient-reported disease activity was assessed using a modified Schnitzler Activity Score¹⁰ in which patients were asked to grade the severity of their total symptoms daily on a scale from 0 (= very good) to 10 (= very bad).

At every clinic visit, serum samples were collected to determine acute phase reactants CRP and serum amyloid A (SAA) levels and patients completed two questionnaires; the Dermatology Life Quality Index (DLQI), a skin disease-specific quality of life questionnaire,

and the SF-36, a generic health-related quality of life instrument, both of which have a recall period of one week. Post-hoc analyses included blood levels of the inflammatory marker S100A12 protein and IL-1 receptor antagonist (IL-1Ra), assessed at days 0, 7 and 120.

Study endpoints

The primary endpoint was the rate of complete clinical responders in the canakinumab-treated group as compared with the placebo group on day 7 of the double-blind phase of the study. Secondary endpoints included the overall clinical response rate, changes in physician (PGA) and patient-reported (Schnitzler activity score) assessments of disease activity, changes in acute phase reactants (CRP, SAA) and changes in quality of life assessments (DLQI and SF-36). Further secondary endpoints were safety of canakinumab treatment assessed by physical examination, routine laboratory markers, vital signs and adverse event reporting. Post-hoc analyses included changes in S100A12 levels and cytokine (IL-1Ra) levels during the study.

Study definitions

A complete clinical response was defined as no or minimal disease activity, i.e. a PGA score ≤ 5 and no greater than 1 in any of the 5 constituent signs/symptoms. A partial clinical response was defined as mild to moderate disease activity with a PGA score > 5 and PGA reduction $\geq 30\%$ as compared with baseline. No clinical response was defined as high disease activity with PGA scores that were increased, stable, or showed $< 30\%$ reduction. Relapse or worsening of clinical symptoms was identified by a $\geq 50\%$ increase in the PGA score as compared with the PGA score 7-14 days after canakinumab initiation.

Statistical analysis

This trial was a pilot study intended to provide information on the efficacy, safety and tolerability of canakinumab in patients with Schnitzler's syndrome, an ultra-rare disease. The sample size reflects the known number of affected patients in Germany. Due to the absence

of randomized trials in this population and the unknown variability of disease activity, statistical power considerations were not applicable.

The difference between the rates of complete clinical responders in the two treatment groups (the primary endpoint) was calculated using Fisher's exact test with a two-tailed significance level of 5%. In the placebo-controlled treatment phase, the differences within treatment groups for PGA Likert scales and blood values were calculated by Wilcoxon signed rank test. For patient-reported outcomes, an independent-samples t-test was applied to test for differences in overall Schnitzler activity scores between canakinumab and placebo, and a paired t-test was used to test for differences in quality of life measurements within treatment groups. The Mann-Whitney U-test was applied to assess differences in changes of clinical scores, inflammation markers and quality of life between the canakinumab and the placebo group. All differences between day 0 and day 120 were analysed by Wilcoxon signed rank test. Correlation was assessed using Spearman's rank correlation. Data are presented either as median with range or mean $\pm$ standard error of the mean (SEM). $P \leq 0.05$ was considered to indicate statistically significant differences. Per protocol, the full analysis and safety set included all subjects with Schnitzler's syndrome who received at least one dose of study medication. All analyses were performed with IBM SPSS version 22.

Results

Study population

Twenty-one patients were screened, and twenty of them underwent randomization and received at least one dose of study drug between July 23rd, 2011 and August 17th, 2012 (**Figure 1**). Of these, 7 were assigned to the canakinumab treatment 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 vs 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 one treatment, completed the double-blind and open-label phase of the study and were included in the primary endpoint analysis and safety analysis.

The percentage of women was slightly higher in the canakinumab group (57%) as compared to the placebo group (38%). At baseline, markers of systemic inflammation (CRP, SAA) were elevated in both groups, with somewhat higher median CRP values in the canakinumab group. Other baseline demographic and clinical characteristics were similar across the study groups (**Table I**). All patients were caucasians, and the median disease duration was 5.5 (range 2 – 22) years. 10 of 20 patients had previously been checked for NLRP3 mutations to exclude late-onset CAPS in the diagnostic work-up. Except for a heterozygous Q703K polymorphism in two patients, which was reported in up to 5% of the general population,¹⁷ no relevant mutations were found. Quantitative baseline paraprotein levels ranged from 318 to 2400 mg/dl for IgM (Ref. 40 – 230 mg/dl) and 776 to 1662 mg/dl for IgG (Ref. 700 – 1600 mg/dl). 8 of 20 patients (3 of them in the canakinumab group and 5 of them in the placebo group) had previously received anakinra and had stopped treatment at least 3 days before day 0. All of them had benefitted from anakinra treatment including one patient with IgA variant paraprotein. Concomitant medication included on demand NSAIDs in most patients and low dose oral corticosteroids (≤ 10 mg of prednisolone equivalent) in single patients.

Clinical efficacy

On day 7, the rate of complete clinical response (primary endpoint), i.e. 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) ($P = 0.001$; **Figure 2A**). Baseline disease activity, as determined by total PGA was comparable in the canakinumab (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 group ($P = 0.018$; **Figure 2B,C**), but not the placebo group. The difference in median changes in PGA total scores (canakinumab -11 vs. placebo 0) was significant between treatment groups ($P < 0.0001$, **Table II**). Patient-assessed disease activity (overall Schnitzler activity score) also showed a marked decline during the first 7 days of treatment (canakinumab -5.5 vs. placebo -1.9). In the canakinumab group, disease activity scores were reduced by 20% within 24h, and significant differences between the two groups were achieved as early as on day three of treatment ($P < 0.05$; **Figure 2D**).

Effects on inflammation markers and interleukin-1 receptor antagonist

Baseline inflammation markers displayed high inter-individual differences. Median serum levels of CRP and SAA in the canakinumab group fell from 9.3 at day 0 to 0.6 mg/dl at day 7 ($P = 0.031$) and from 428 to 13 mg/l ($P = 0.031$), respectively, but increased in the placebo group from 3.1 to 5.0 mg/dl for CRP ($P = 0.685$) and 160 to 211 mg/l for SAA ($P = 0.733$) (**Figure 3A,B**). Median S100A12 levels were reduced from 969 to 189 ng/ml ($P = 0.016$) in canakinumab-treated patients, but did not change significantly with placebo ($P = 0.734$) after the first week of treatment (**Figure 3C**). Median serum levels of interleukin-1 receptor antagonist (IL-1Ra), a biomarker of autoinflammatory disorders, were increased before treatment, and fell from 1026 pg/ml at baseline to 562 pg/ml at day 7 in the canakinumab group ($P = 0.016$), but did not decline in the placebo group ($P = 0.641$) (**Figure 3D**). The changes of CRP, SAA and IL-1Ra levels were significantly different between treatment groups (**Table II**).

Effects on quality of life

Quality of life was considerably impaired at baseline and similar in both treatment groups. Within the first week, canakinumab significantly reduced mean DLQI sum scores from moderate (8.2 ± 2.4) to mild impairment (2.8 ± 1.7 ; $P = 0.003$) and improved SF-36 mean physical component summary scores from moderate impairment (32.8 ± 4.6) to normal values (46.6 ± 3.0 ; $P = 0.008$) (**Figure 4**). There were no significant changes of 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 ($P < 0.0001$; **Table II**).

Open-label phase

During the open-label phase of the study, all of the patients who switched to canakinumab therapy improved, and the patients who stayed on canakinumab treatment improved further. Seven to fourteen days after canakinumab initiation, 15 of 20 patients were complete clinical responders and the remaining 5 were partial responders. At day 120, disease activity scores (PGA), inflammation markers and quality of life scores (DLQI, SF-36) were all significantly reduced as compared to baseline (**Table III**). Canakinumab doses during the open-label phase were based on individual clinical and laboratory responses. 8 patients with complete clinical response and normalized CRP levels 7 days after treatment initiation continued with canakinumab 150 mg doses. 12 patients received canakinumab 300 mg doses because of slightly elevated inflammation markers and/or remaining mild to moderate disease activity after canakinumab 150 mg initiation. The duration of clinical improvement after canakinumab administration showed major inter-individual and some intra-individual differences. In total, 14 of 20 patients experienced relapse of clinical symptoms and received one to three further canakinumab injections within the first 16 weeks of the study (**Figure 5**). Disease relapse or recurrence of subclinical inflammation also accounted for moderately elevated inflammation

markers in single patients at day 120. There was no significant difference in the duration of clinical improvement between the canakinumab 150 mg and 300 mg dose groups. The monoclonal gammopathy persisted in all participants, and no significant changes in paraprotein levels occurred during the study period. From baseline to day 120, median IgM levels marginally increased from 560 to 634 mg/dl, and median IgG levels slightly decreased from 1,219 to 1,094 mg/dl.

Adverse events

There were 31 adverse events in 17 patients, six during the screening period, none in the placebo-controlled phase, and 25 during the open-label part including 3 serious AEs (2 hypertensive episodes in one patient with concomitant oral corticosteroid medication and severe lumbago with hospitalization in another patient). The other 22 adverse events during canakinumab open-label treatment were mild or moderate and included infections (e.g. respiratory [n=10] and urinary tract [n=2]), gastrointestinal complaints (n=3), non-specific pain (n=2), skin symptoms (pruritus [n=1], methicillin-resistant staphylococcus aureus colonization [n=1]), osteochondrosis (n=1), asthma (n=1) and weight gain (n=1). No significant changes of safety laboratory parameters were observed, and canakinumab injections were well tolerated without noticeable injection site reactions.

Discussion

In this 4-month placebo-controlled study, canakinumab significantly improved the clinical signs and symptoms of Schnitzler's syndrome, reduced inflammation markers, and improved quality of life. By using the PGA score that combines the 5 key symptoms of Schnitzler's syndrome, i.e. urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain, we demonstrated that all patients benefitted from canakinumab treatment, and all clinical symptoms except fever were significantly improved after the first week of therapy. The absence of significant changes in fever scores may be explained by its episodic nature; only 9 of 20 patients had fever at day 0. Canakinumab's rapid onset of action with 20% improvement in overall Schnitzler activity scores within 24h confirms earlier observations in CAPS and Schnitzler's syndrome that clinical effects of canakinumab treatment first appeared after 6-24h.^{11, 14}

In autoinflammatory diseases, continuous inflammation is known to be associated with an increased risk of permanent tissue damage such as amyloidosis.¹⁸ The significant reduction in CRP and SAA levels in all canakinumab-treated patients within 7 days and normalization of median CRP levels at day 120 indicate effective control of inflammation and support previous reports in CAPS patients.^{14, 19}

Phagocyte-specific S100 proteins A8/9 and A12 are known to be sensitive markers of disease activity and inflammation in autoinflammatory disorders including Schnitzler's syndrome.²⁰⁻²² In our patient cohort, S100A12 baseline values ranged between those reported for CAPS (ca. 150-700 ng/ml) and systemic juvenile idiopathic arthritis (ca. 7000 ng/ml).²³ The changes in S100A12 levels significantly correlated with changes in PGA urticarial rash scores but not with PGA total scores or CRP and SAA levels. As urticarial rash is among the first symptoms in disease exacerbations of Schnitzler's syndrome and S100A12 is a known danger molecule and chemoattractant to mast cells,²⁴ our results suggest that S100A12 proteins may play a crucial role in the early flare reaction by activating skin mast cells which are known to induce the IL-1 β -mediated urticarial rash in Schnitzler's syndrome and CAPS.^{25, 26}

As of now, no biomarkers are established to assess Schnitzler's syndrome patients for changes in disease activity in response to treatment. IL-1 β is the key inflammatory mediator in Schnitzler's syndrome. Its secretion from peripheral blood mononuclear cells is increased in patients with Schnitzler's syndrome and is inhibited *ex vivo* and *in vivo* by IL-1 blockade.⁹

²⁷ As IL-1 β in the serum is virtually undetectable, we measured serum levels of IL-1Ra, which is produced at steady state levels with the IL-1 receptor and inhibits the pro-inflammatory cytokines IL-1 α and IL-1 β by non-productively binding to the IL-1 receptor. Following IL-1 β neutralization in CAPS patients, IL-1Ra serum levels were shown to be downregulated within a few days.²⁸ In our study, changes in IL-1Ra levels and disease activity in response to canakinumab correlated well, suggesting that IL-1Ra may be a good biomarker for monitoring disease activity in patients with Schnitzler's syndrome. Possibly, the high clinical disease activity in single patients with only modest CRP and SAA elevations may be explained by excessive IL-1Ra levels.

Patients with autoinflammatory conditions including Schnitzler's syndrome often suffer from considerable quality of life impairment. In our patients, baseline DLQI scores were comparable to those reported for other chronic skin disorders including chronic urticaria (9.9)²⁹ and urticarial vasculitis (9.2).³⁰ Interestingly and in line with previous results from Schnitzler's syndrome patients,¹¹ the assessment of SF-36 baseline scores revealed physical health to be clearly compromised but mental health to be less affected. Analysis of SF-36 subdomains shows pain to be a major inducer of quality of life impairment, which is mirrored by high PGA scores for the key symptoms myalgia and arthralgia/bone pain. Also, the great improvement of physical health-related quality of life scores and the almost complete restoration of skin-related quality of life at day 120 underscores the efficacy of canakinumab treatment.

Some intra-individual differences in time to relapse after canakinumab administration may be explained by seasonal variations with more pronounced symptoms during winter or infections triggering disease activity. In accordance with earlier findings,¹¹ we observed considerable inter-individual variability in the duration of clinical improvement that was not closely linked to disease activity scores or inflammation markers.

Respiratory tract infections were the most frequent AEs in our study, which is in line with the results of earlier canakinumab studies in CAPS patients.^{14, 19} Although respiratory tract infections are very common in the general population, it cannot be excluded that these infections may have been facilitated by the anti-IL-1 treatment. Thus, patients on IL-1 blockade should be closely monitored for potential infections and adequately treated to prevent complications. This also includes common vaccinations such as influenza and pneumococcal infections, which are recommended prior to start of long-term anti-IL-1 treatment. The 3 SAEs, 2 hypertensive episodes in one Schnitzler's syndrome patient with concomitant oral corticosteroid use and known hypertensive disease as well as severe lumbago with subsequent hospitalization in another patient, were not considered to be drug related. Still, as hypertension is very common in the elderly population, it will be important to closely monitor the effect of canakinumab on blood pressure and possible drug interactions in future clinical trials. This study has several strengths and limitations. The latter include the number of patients enrolled in this trial. However, this is by far the biggest clinical trial in Schnitzler's syndrome, an ultra-rare disease. In addition, the placebo-controlled phase of 7 days was short, but to withhold effective treatment for longer than this would have been unethical, and patients in the canakinumab group showed marked and significant improvement during this first week of treatment. The imbalance in randomization with 7 canakinumab-treated and 13 placebo-treated patients is another limitation, but is unlikely to affect the study results as all patients responded well to canakinumab open-label treatment. Also, our results are preliminary in the sense of treatment duration and have to be interpreted with care as the open label treatment phase of this study is still ongoing. Therefore, long-term efficacy and safety are further monitored, and detailed results will be reported upon

study completion. The major strength of this study is its placebo-controlled design, making it the first and as of yet only randomized controlled trial in Schnitzler's syndrome. This primary multi-center study confirms the marked efficacy of previous case reports and small open-label studies on IL-1 blockade in this condition,^{10, 11, 31} which facilitates the treatment of patients with Schnitzler's syndrome and encourages the use of canakinumab or other IL-1 targeting treatments in this disease. In comparison to anakinra (4 – 6 hours) and rilonacept (67 hours – 7 days), canakinumab has a longer half-life (21 - 28 days) and exclusively binds to IL-1 β , the key inflammatory mediator in Schnitzler's syndrome, but not to IL-1 α or the IL-1 receptor. Besides the advantage of less frequent dosing with canakinumab, injection site reactions (which were absent in our study) are less often reported as compared with anakinra and rilonacept.³² In conclusion, our study results show good efficacy of canakinumab treatment against placebo in reducing the clinical symptoms, inflammation markers and enhancing quality of life in patients with symptomatic Schnitzler's syndrome. Over the limited four month duration of this study, canakinumab treatment appeared to be safe and well tolerated. Treatment of greater patient numbers and long-term administration are necessary in order to further evaluate the efficacy and safety of canakinumab treatment in Schnitzler's syndrome.

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Conflict of interest

KK reports grants and personal fees from Novartis, during the conduct of the study; grants and personal fees from Novartis, grants from Regeneron, personal fees from Roche, outside the submitted work.

AT has nothing to disclose.

NW has nothing to disclose.

JF has nothing to disclose.

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MKC has nothing to disclose.

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Tables

Table I: Baseline demographic, clinical and laboratory characteristics across the study groups. * Data are expressed as median with range.

	Canakinumab	Placebo
Age* (years)	62 (54 – 71)	64 (28 – 74)
Sex (n)	F/M: 4/3	F/M: 5/8
Disease duration* (years)	5.5 (3 – 13.5)	6.3 (1.5 – 22)
Clinical symptoms: (n)		
Urticarial rash	7/7	13/13
Fatigue	6/7	13/13
Fever	3/7	6/13
Myalgia	7/7	11/13
Arthralgia/bone pain	7/7	13/13
Paraproteins: (n)		
IgM kappa	5/7	9/13
IgM lambda	0/7	1/13
IgG kappa	1/7	1/13
IgG lambda	0/7	2/13
IgA lambda	1/7	0/13
CRP* in mg/dl (Ref. <0.5)	9.3 (1.4 - 25.4)	3.1 (0.7 – 13.9)
SAA* in mg/l (Ref. <6)	428 (69 – 857)	160 (2 – 1310)
S100A12* in ng/ml (Ref. <200)	969 (151 – 1797)	626 (151 – 3036)
IL-1Ra* in pg/ml (Ref. <500)	1026 (262 – 5189)	1846 (1093 – 10027)

Table II: Changes in disease activity, quality of life impairment, inflammation markers and interleukin-1 receptor antagonist levels in canakinumab and placebo patients from baseline to day 7, the end of the double blind treatment phase. Data are expressed as median with range.

	Canakinumab	Placebo	P value
PGA scores:			
Total (0-20)	-11 (-18 to -3)	0 (-8 to 5)	< 0.0001
Urticarial rash (0-4)	-3 (-4 to -1)	0 (-2 to 2)	< 0.0001
Fatigue (0-4)	-2 (-4 to 0)	0 (-3 to 1)	= 0.015
Fever/Chills (0-4)	0 (-4 to 0)	0 (-1 to 2)	= 0.065
Myalgia (0-4)	-3 (-4 to 0)	0 (-2 to 3)	= 0.001
Arthralgia/Bone pain (0-4)	-3 (-4 to 0)	0 (-2 to 1)	= 0.004
Acute phase reactants:			
CRP in mg/dl (Ref. <0.5)	-7.99 (-24.28 to -0.49)	0.08 (-3.65 to 6.26)	= 0.002
SAA in mg/l (Ref. <6)	-389.65 (-817.1 to -64.6)	-13.4 (-1003 to 423,8)	= 0.032
S100A12 in ng/ml (Ref. <200)	-723 (-837 to -119)	290 (-911 to 973)	= 0.055
IL-1Ra in pg/ml (Ref. <500)	-645 (-4282 to -33)	294 (-8028 to 1607)	= 0.037
DLQI sum scores (0-30)	-5 (-10 to 1)	0.5 (-3 to 8)	< 0.0001
SF-36 scores (0-100):			
Physical component sum	13 (3 to 32)	-1 (-9 to 5)	< 0.0001
Physical function	10 (0 to 90)	0 (-25 to 20)	= 0.032
Role physical	50 (0 to 100)	0 (-50 to 25)	= 0.001
Bodily pain	32.5 (10 to 68)	0 (-23 to 30)	= 0.003
General health	10 (5 to 25)	-5 (-30 to 10)	= 0.001
Mental component sum	1 (-8 to 24)	-1 (-14 to 8)	= 0.351
Mental health	12 (0 to 36)	0 (-32 to 20)	= 0.014
Role emotional	0 (0 to 100)	0 (-100 to 33)	= 0.392
Social function	12.5 (0 to 75)	0 (-50 to 25)	= 0.208
Vitality	15 (10 to 30)	0 (-35 to 20)	= 0.001

Table III: Clinical and laboratory efficacy during open-label canakinumab treatment.

Data are expressed as median with range.

	Baseline (day 0)	Canakinumab open-label (day 120)	P value
PGA total scores	14.5 (8 - 20)	3.5 (0 - 9)	< 0.0001
Acute phase reactants			
CRP in mg/dl (Ref. <0.5)	6.09 (0.7 - 25.4)	0.3 (0.04 - 6.24)	< 0.0001
SAA in mg/l (Ref. <6)	180 (1.9 - 1310)	13.3 (4.6 - 409)	= 0.001
S100A12 in ng/ml (Ref. <200)	901 (151 - 3036)	113 (20 - 3470)	= 0.041
IL-1Ra in pg/ml (Ref. <500)	1592 (262 - 10027)	583 (283 - 1401)	= 0.001
DLQI sum scores (0-30)	8.5 (1 - 21)	1 (0 - 25)	= 0.006
SF-36 scores (0-100)			
Physical component summary	28.8 (33.7)	47.0 (42.7)	= 0.003
Mental component summary	47.0 (31.62)	50.7 (34.7)	= 0.058

Figure legends

Figure 1: Subject disposition showing the number of screened, randomized and completed patients.

Figure 2: Changes in disease activity. **A)** Responder rates at day 7. Red = complete responders and pink = partial responders to canakinumab. Light blue = partial responders to placebo. Grey = non-responders. Absolute patient numbers are indicated in the bars. **B)** Physician global assessment (PGA). The light grey areas indicate minimal disease activity. **C)** Representative patient images. **D)** The overall Schnitzler activity score for 7 days before and 7 days following treatment with canakinumab 150 mg or placebo. Asterisks indicate a significant ($*P \leq 0.05$; $**P \leq 0.01$) difference from placebo. Changes in overall Schnitzler activity scores correlated with changes in total PGA scores ($r = 0.595$, $P = 0.012$).

Figure 3: Changes in inflammation markers and IL-1Ra levels. **A)** CRP levels. **B)** SAA levels. **C)** S100A12 levels. **D)** IL-1Ra levels. The light grey areas indicate normal values. Changes in CRP, SAA and IL-1Ra levels correlated with changes in total PGA scores (CRP: $r = 0.748$, $P < 0.0001$; SAA: $r = 0.585$, $P = 0.011$; IL-1Ra: $r = 0.600$, $P = 0.018$). Changes in S100A12 values followed changes in PGA urticarial rash scores ($r = 0.556$, $P = 0.025$) but not PGA total scores.

Figure 4: Changes in quality of life scores. **A)** DLQI scores. **B)** SF-36 physical component summary scores. **C)** SF-36 mental component summary scores. The light grey areas indicate reference values (physical component 44.81; mental component 53.18) of an age-matched (61-70 years) German healthy population. Changes in DLQI sum scores and SF-36 physical component summary scores correlated with changes in PGA total scores (DLQI: $r = 0.487$, $P = 0.034$; SF-36 physical component summary: $r = 0.780$, $P < 0.0001$).

587 **Figure 5:** Individual duration of clinical improvement following canakinumab administration
588 during open-label treatment. Red arrows indicate individual time points of relapsing
589 symptoms and subsequent canakinumab treatment. Asterisks indicate ongoing clinical
590 improvement beyond day 120.

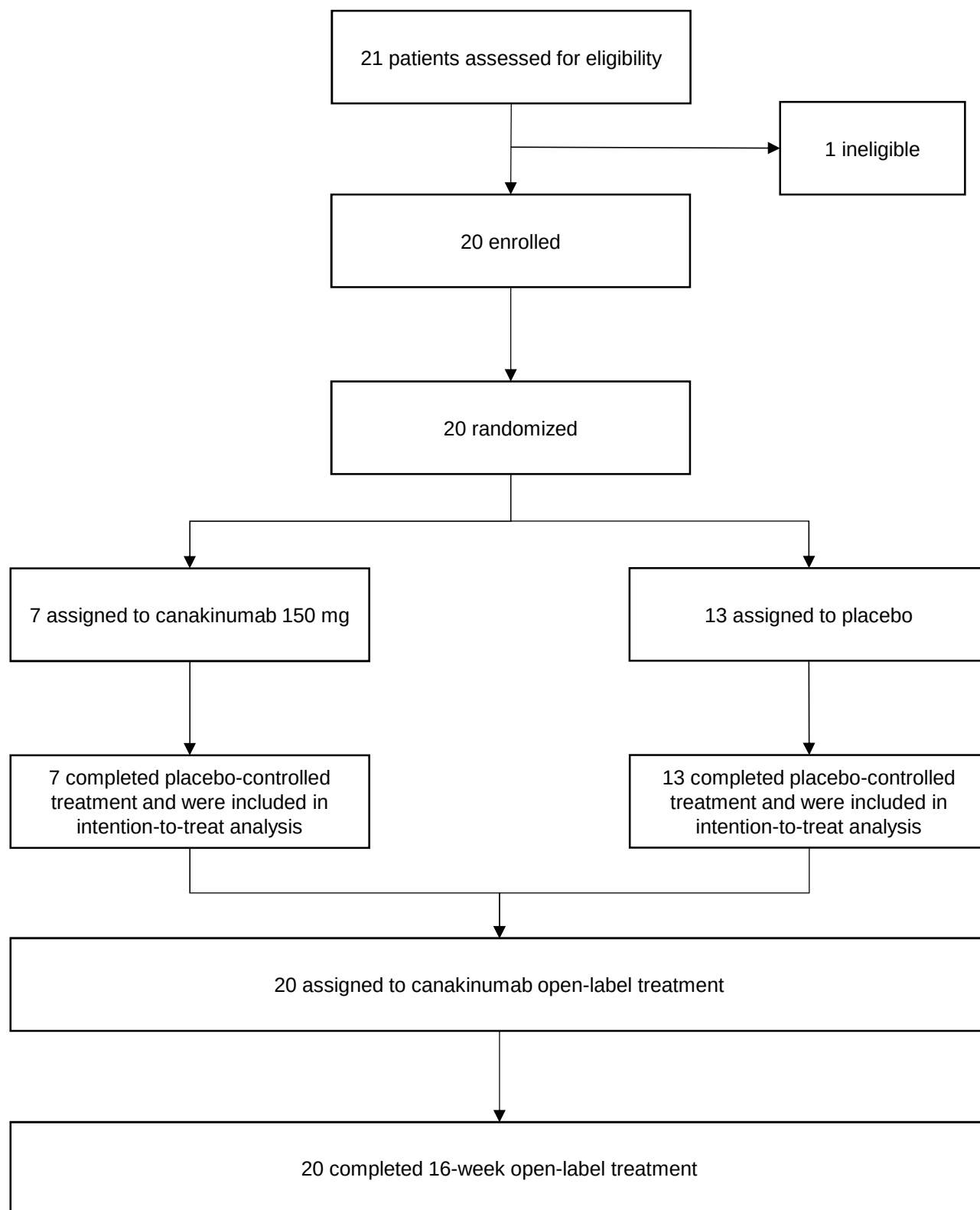


Figure 1

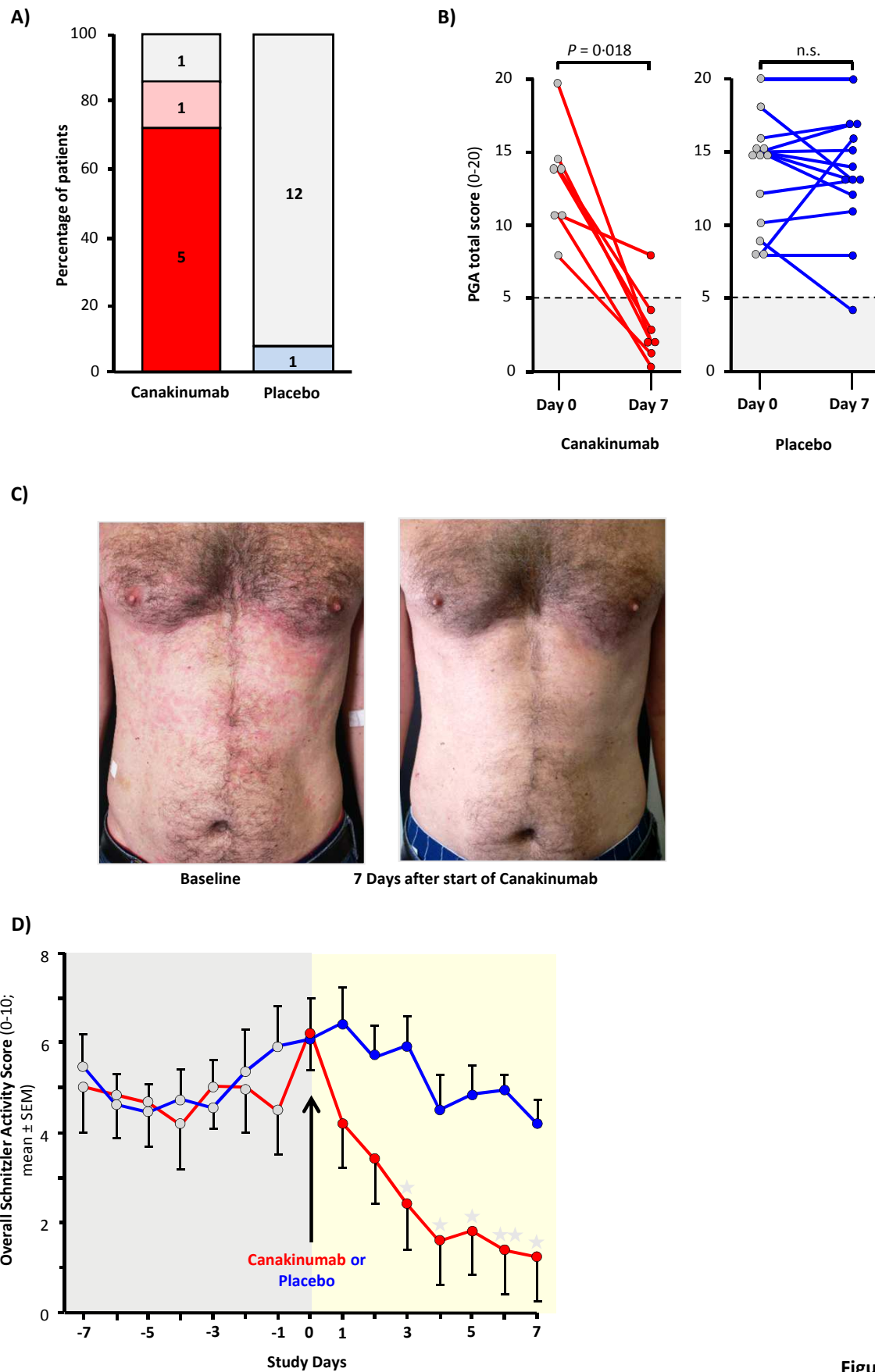


Figure 2

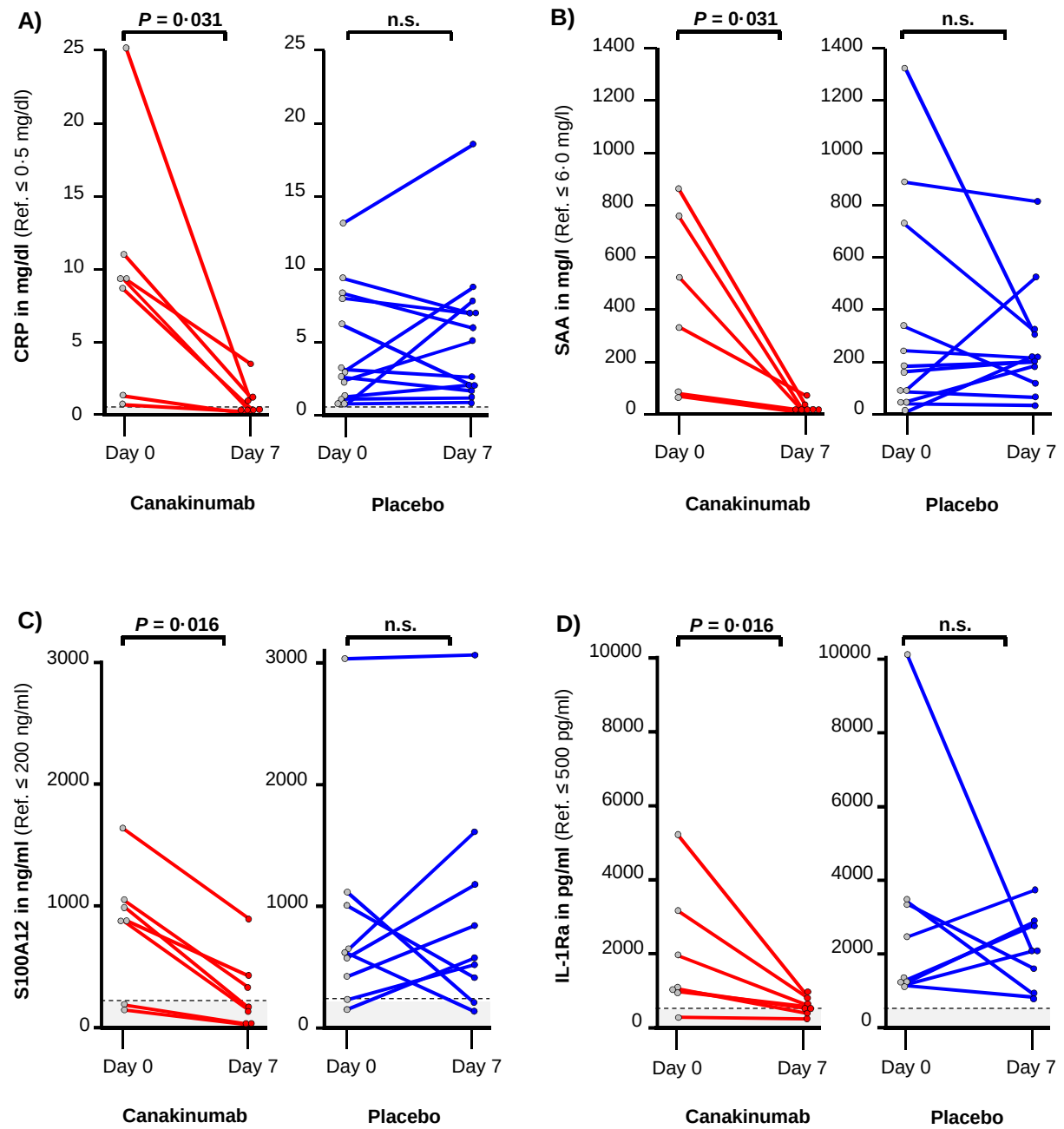


Figure 3

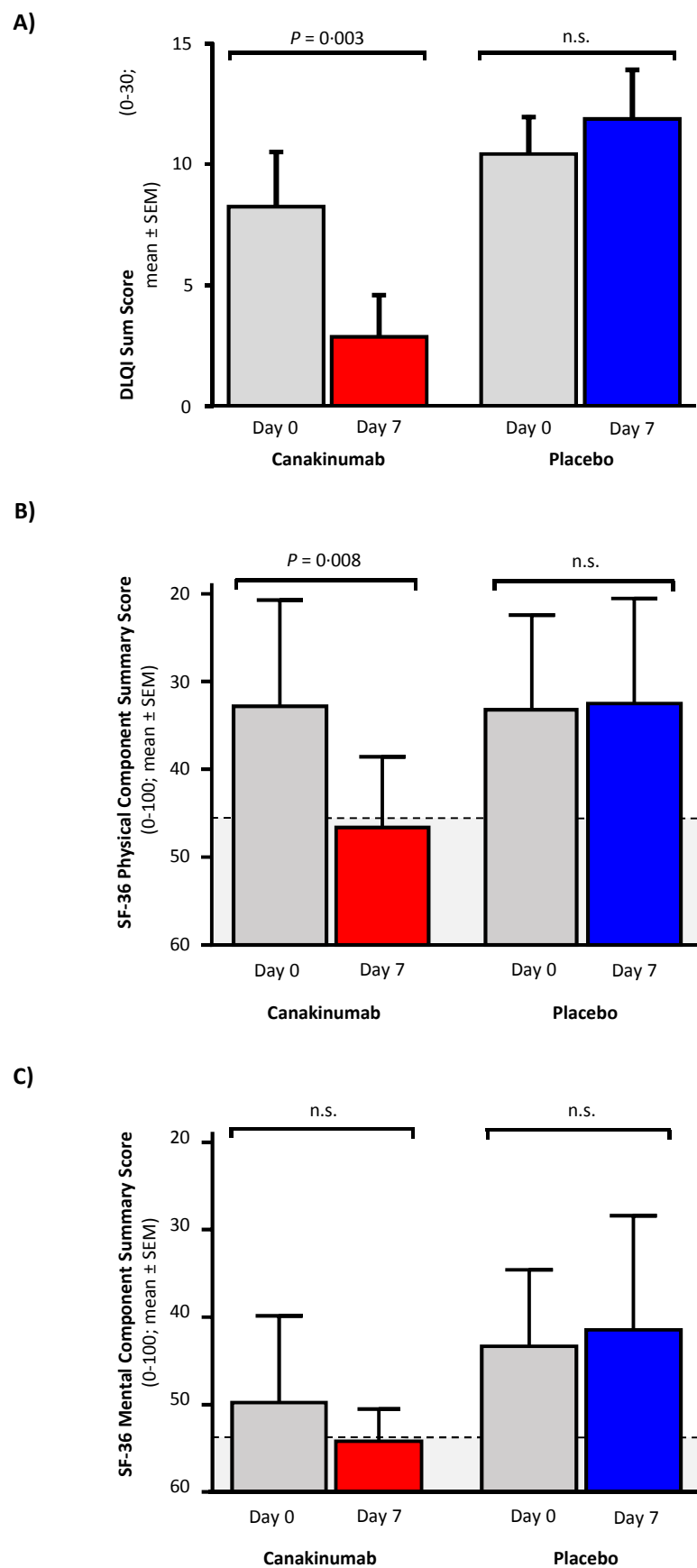


Figure 4

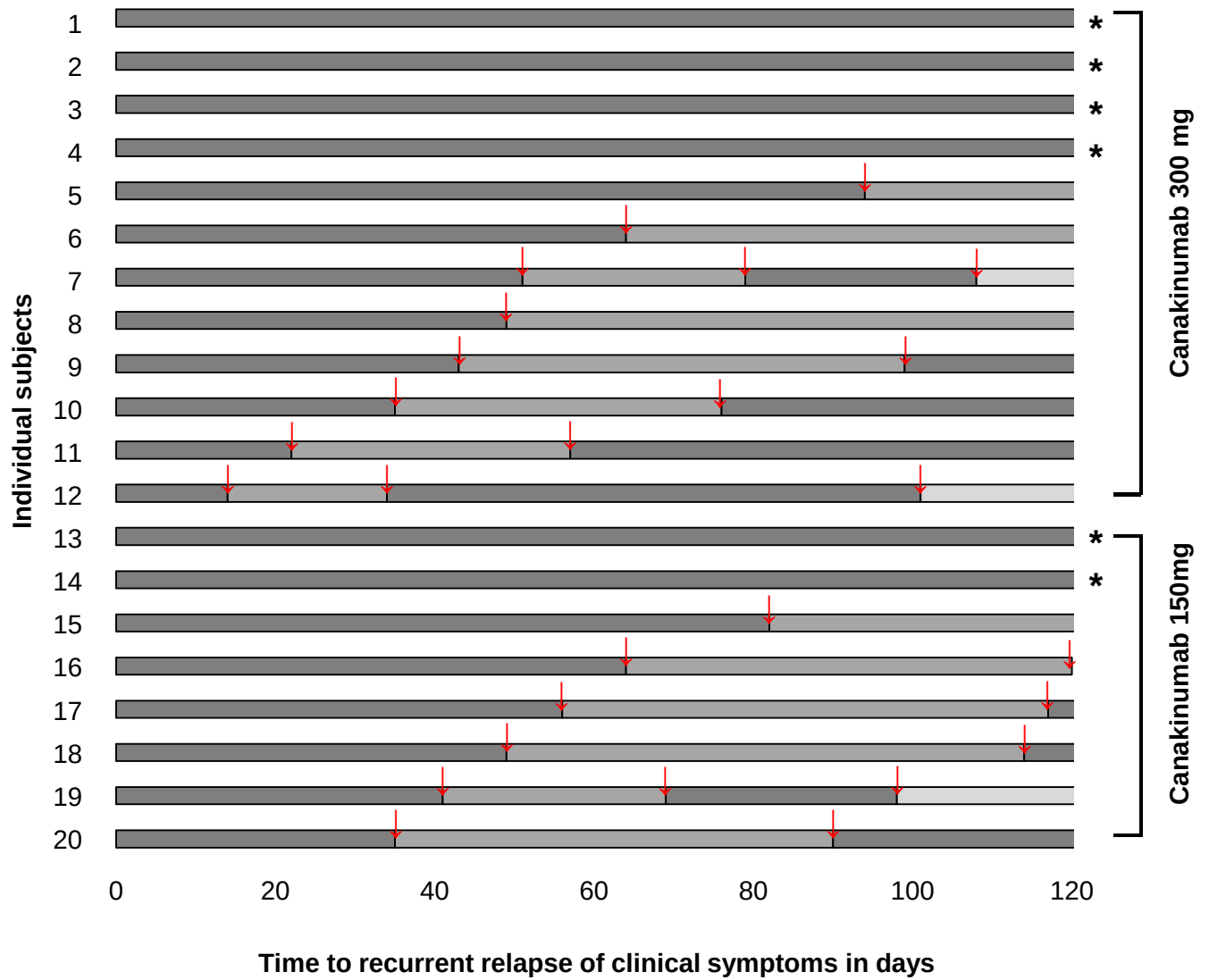


Figure 5