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**Improvement in patient-reported outcomes in rheumatoid arthritis patients treated with sarilumab is independent of the cognition levels**

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Patients with rheumatoid arthritis (RA) are prone to cognitive decline and mental problems, reducing their functional capabilities and adherence to treatment [1-4]. Patient-reported outcomes (PROs) are being increasingly recognized as important tools in RA management [5]. Sarilumab is an interleukin-6 receptor antagonist, approved in adult patients with moderate-to-severe RA and inadequate response or intolerance to disease-modifying antirheumatic drugs (DMARDs) [6]. SariPRO (**Sarilumab on Patient-Reported Outcomes**; NCT03449758) – a French, multicenter, open-label, single-arm, phase-IV study, assessed the effect of sarilumab on PROs in RA patients, focusing on cognition.

SariPRO enrolled patients with active moderate-to-severe RA despite treatment with DMARDs or anti-tumor necrosis factor from March-December 2018. Patients received sarilumab 200 mg every 2 weeks (W), monotherapy or in combination with methotrexate/DMARDs for 24W (**Supplementary Fig. S1**). Patients with prior exposure to sarilumab were excluded. The primary efficacy endpoint was the change from baseline to 24W in the total RA impact of disease (RAID) score. Changes in PROs for different RA domains (cognition, anxiety, depression, fatigue, disability index, and physical activity; **Supplementary Table S1**) and disease activity (erythrocyte sedimentation rate [ESR], disease activity score 28-ESR [DAS28-ESR], and clinical disease activity index [CDAI]) were evaluated over 24W. The impact of baseline cognition level on DAS28-ESR scores was assessed (exploratory analysis).

Eighty-four patients were enrolled (mean [standard deviation, SD] age, 59.1 [12.3] years; females, 75%; **Table 1** and **Supplementary Fig. S2**). Patients shared the main characteristics expected; 26 (31%) patients had low cognition (Multidimensional Assessment of Thymic States score <18; **Table 1**). Sarilumab treatment significantly decreased the total RAID score from baseline through W4 (4.6 [2.1]), W12 (3.9 [2.3]), and W24 (3.3 [2.5]) (**Table 2**;  $P < 0.05$ ), with sustained improvements in individual domain scores and disease activity over 24W (**Supplementary Fig. S3**). Other PROs (except cognition) also showed improvements over 24W treatment, with approximately 70% reduction in duration of morning stiffness (**Table 2** and **Supplementary Table S2**). Cognition level had no impact on clinical response or remission rate (**Table 1**). Patients with moderate-to-severe depression (hospital anxiety and depression score  $\geq 11$ ) demonstrated greater deterioration in the DAS28-ESR scores and CDAI (median [interquartile range]: -3.3 [-4.1; -2.5],  $P = 0.07$  and -19.7 [-30.4; -12.0],  $P = 0.06$ , respectively) versus those with mild depression. Sarilumab's safety profile was as expected.

Congruent with clinical trial data [7, 8], sarilumab (monotherapy/combotherapy) significantly improved the RAID scores and other PROs and disease activity in RA patients over 24W. A substantial proportion of patients had cognition decline, which was not associated

with sarilumab's effect on disease activity, implying that blocking the interleukin-6 pathway had no effect on cognition. The study strengths were inclusion of patients from a real-life setting and PROs covering a myriad of RA symptoms/signs, while its limitations were the lack of a control/comparison arm and small sample size. In conclusion, sarilumab treatment substantially improved disease activity (as assessed by PROs) in real-life RA patients. Although these findings are exploratory, they confirm and emphasize the need for holistic care for RA patients, including attention to their mental health.

**Table 1.** Patient demographics and baseline disease characteristics.

<b>Characteristics</b>	<b>Total (N = 84)</b>	
Age, years, mean (SD)	59.1 (12.3)	
Female, <i>n</i> (%)	63 (75.0)	
BMI, kg/m <sup>2</sup> , mean (SD)	25.9 (5.8)	
Prior biologic therapies or targeted synthetic DMARDs use for RA, <i>n</i> (%)	35 (41.7)	
Patients receiving methotrexate at baseline, <i>n</i> (%)	57 (82.6)	
Rheumatoid factor positive, <i>n</i> (%)	61 (81.3)	
Anti-CCP positivity, <i>n</i> (%)	64 (84.2)	
RAID score, mean (SD)	5.8 (1.9)	
HADS anxiety score, mean (SD)	8.1 (4.3)	
HADS depression score, mean (SD)	7.0 (3.9)	
MAThYS scale cognition score, mean (SD)	18.2 (4.9)	
FACIT-F total score, mean (SD)	25.5 (10.3)	
HAQ-DI total score, mean (SD)	1.3 (0.8)	
IPAQ total score, mean (SD)	1759.9 (1185.0)	
PGA <sup>a</sup> of disease activity (0–100)	61.0 (20.7)	
Duration of morning stiffness, minutes, mean (SD)	72.3 (75.0)	
ESR, mm/h, mean (SD)	28.8 (23.4)	
SJC, mean (SD)	6.3 (5.1)	
TJC, mean (SD)	7.3 (5.8)	
DAS28-ESR (>3.2: moderate-to-severe disease activity), mean (SD)	5.0 (1.2)	
CDAI, mean (SD)	22.5 (11.2)	
<b>Patient demographics and baseline disease characteristics according to MAThYS cognition levels</b>		
<b>Characteristics</b>	<b>Inhibition (&lt;18) N = 26</b>	<b>Normal and activation (≥18) N = 52</b>
Age using the quartiles, <i>n</i> (%)		
≤51 years	6 (23.1)	16 (30.7)
51–60.5 years	10 (38.5)	6 (11.5)
60.5–68.5 years	3 (11.5)	16 (30.7)
>68.5 years	7 (26.9)	14 (27.0)
Gender, female (%)	18 (69.2)	41 (78.8)
RA duration using the quartiles, <i>n</i> (%)		
Q1: ≤2.2 years	5 (19.2)	14 (26.9)
Q2: 2.2–6.6 years	6 (23.1)	14 (26.9)
Q3: 6.6–14.5 years	8 (30.8)	11 (21.2)

Q4: >14.5 years	7 (26.9)	13 (25.0)
Rheumatoid factor positive, <i>n</i> (%)	18 (75.0)	41 (78.9)
PGA (VAS 0–100), mean (SD)	65.3 (21.2)	59.1 (23.2)
Depression evaluated by HADS, <i>n</i> (%)	18 (69.2)	16 (30.8)
Anxiety evaluated by HADS, <i>n</i> (%)	17 (65.4)	21 (40.5)
MAThYS global score, mean (SD)	72.6 (21.0)	98.3 (11.5)
FACIT-F score using the quartiles, <i>n</i> (%)		
Q1: ≤18.4	4 (15.4)	17 (32.7)
Q2: 18.4–27	8 (30.8)	12 (24.0)
Q3: 27–32.5	6 (23.1)	11 (21.3)
Q4: >32.5	8 (30.8)	10 (19.2)
DAS28 in classes using the quartiles, <i>n</i> (%)		
Q1: ≤3.9	5 (20.0)	16 (30.8)
Q2: 3.9 to 4.9	5 (20.0)	13 (25.0)
Q3: 4.9 to 5.8	9 (36.0)	11 (21.2)
Q4: >5.8	6 (24.0)	11 (21.2)

BMI, body mass index; CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; DAS, disease activity scores; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; FACIT-F, functional assessment of chronic illness therapy – fatigue; HADS, hospital anxiety and depression scale; HAQ-DI, Stanford health assessment questionnaire – disability index; IPAQ, international physical activity questionnaire; MAThYS, Multidimensional Assessment of Thymic States; PGA, patient global assessment; Q, quarter; RA, rheumatoid arthritis; RAID, RA impact of disease; SD, standard deviation; SJC, swollen joints count; TJC, tender joints count; VAS, visual analog scale.

<sup>a</sup>PGA of disease activity was assessed using a 100 mm VSA (0 – no pain to 100 – maxima pain imaginable).

**Table 2.** Change in the total score of the PROs and MAThYS cognition score from baseline to each assessment (*N* = 84).

Parameter	Baseline	Week 4	Week 12	Week 24
RAID	5.8 (1.9)	4.6 (2.1)	3.9 (2.3)	3.3 (2.5)
MAThYS cognition score	18.2 (4.9)	18.5 (4.8)	19.4 (3.4)	18.2 (5.1)
HADS anxiety	8.1 (4.3)	7.2 (4.3)	6.1 (3.7)	6.6 (3.9)
HADS depression	7.0 (3.9)	6.6 (4.0)	5.7 (4.1)	5.5 (4.1)
FACIT-F	25.5 (10.3)	21.0 (10.5)	18.8 (9.7)	17.9 (11.4)
HAQ-DI	1.3 (0.8)	1.1 (0.7)	0.8 (0.7)	0.8 (0.8)
PGA of disease activity (0–100 mm VAS)	61.1 (22.4)	44.1 (25.6)	36.6 (26.7)	34.6 (25.6)
Duration of morning stiffness (minutes)	72.3 (75.0)	34.7 (43.9)	28.9 (47.2)	21.3 (37.5)
IPAQ	1759.9 (1185.0)	1881.1 (1203.9)	2061.0 (1266.9)	2089.5 (1476.4)

FACIT-F, functional assessment of chronic illness therapy – fatigue; HADS, hospital anxiety and depression scale; HAQ-DI, Stanford health assessment questionnaire – disability index; IPAQ, international physical activity questionnaire; MAThYS, Multidimensional Assessment of Thymic States; PGA, patient global assessment; PROs, patient-reported outcomes; RAID, rheumatoid arthritis impact of disease; SD, standard deviation; VAS, visual analogue scale.

All the values are presented in mean (SD).

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This study was sponsored by Sanofi. The authors designed the study and have access to all the data.

## Data availability

Qualified researchers may request access to patient-level data and related documents (e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on the data-sharing criteria of Sanofi, eligible studies, and process for requesting access can be found at <https://vivli.org/>.

## Disclosures of interest

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**Thierry Schaefferbeke** has nothing to declare.

**Marmar Kabir-Ahmadi** was an employee of CorEvitas, LLC at the time this analysis was conducted and has nothing to declare.

**Florence E Lévy-Weil** is an employee of Sanofi and may hold stock and/or stock options in the company.

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## Improvement in patient-reported outcomes in rheumatoid arthritis patients treated with sarilumab is independent of the cognition levels

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## Supplementary material

### Supplementary Table S1. Patient-reported outcome questionnaires

Questionnaires	Description
Rheumatoid arthritis impact of disease (RAID) score	The RAID questionnaire comprises seven domains: pain, functional disability, fatigue, physical and psychological wellbeing, sleep disturbance and coping. Each domain was evaluated using a single question answered on a 0 to 10 numerical rating scale. Each domain has a specific weight assigned



## SariPRO Supplementary data

	per a patient survey. The RAID score is a continuous variable ranging from 0 (best) to 10 (worst).
Hospital anxiety and depression scale (HADS)	The HADS questionnaire comprises 14 items divided into 2 subscales: anxiety and depression. Each item has a rating from 0 to 3, leading to the maximum score of 21 points for anxiety and depression. A total score of up to 19 indicates a major depressive episode; a total score of up to 13 indicates adjustment disorders and minor depression.
Multidimensional Assessment of Thymic States (MAThys)	It is a multi-dimensional, self-administered questionnaire comprising 20 items corresponding to five dimensions (emotional reactivity, cognition, psychomotor function, motivation, and sensory perception) as perceived by patients for the preceding week. Each item is set out as a continuous measure in the form of a visual analog scale (VAS) of 10 cm on which the patient is asked to make a mark to indicate where they are positioned between the two predefined extreme propositions.
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)	It is a symptom-specific scale that measures fatigue in patients, assessed by chronic illness therapy over the 7 preceding days. This scale comprises 13 items, scored on a 5-point Likert scale, from 0 (not at all) to 4 (very much). The figures are reversed during score calculations so that a higher score indicates more favorable conditions. Total scores range from 0 to 52, with lower scores representing greater fatigue.
Stanford Health Assessment Questionnaire – Disability Index (HAQ-DI)	It is a patient-oriented outcome assessment questionnaire, specifically developed to assess the extent of functional ability in patients with RA. It consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. There are two or three questions for each component, with scoring within each component ranging from 0 (without any difficulty) to 3 (unable to do). The eight component scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled). It is not truly continuous but has 25 possible values.
International Physical Activity Questionnaire (IPAQ)	It is a 27-item self-reported questionnaire designed to measure the physical activity of patients. It comprises several parts (job-related, transport-related and at-home and leisure-time physical activity) and intensities (moderate, vigorous, and mild) and includes sitting time. Based on frequency, duration and intensity of self-reported physical activity, individuals are categorized into low, moderate, and high physical activity groups.
Patient global assessment (PGA) of disease activity	Measures RA activity as perceived by the patient, using a 100-mm horizontal VAS.
Duration of morning stiffness (in min)	Self-reported by patients with RA

## SariPRO Supplementary data

HADS, hospital anxiety and depression scale; HAQ-DI, Stanford health assessment questionnaire – disability index; RA, rheumatoid arthritis; RAID, rheumatoid arthritis impact of disease; VAS, visual analogue score.

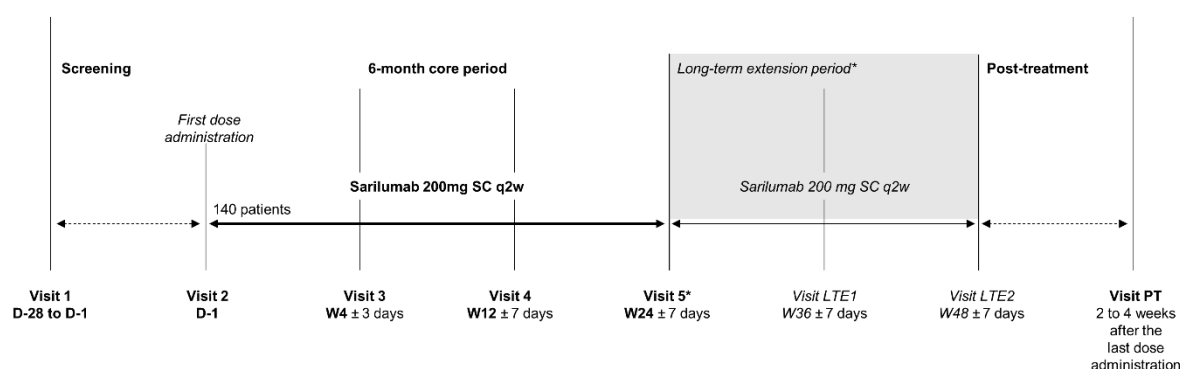
**Supplementary Table S2.** Change in MATHyS scale total score and subscores from baseline to each assessment – ITT population ( $N = 84$ )

Parameter	Baseline	Week 4	Week 12	Week 24
MATHyS scale total score	88.4 (21.1)	89.6 (20.3)	94.8 (13.6)	90.9 (22.3)
Emotion score	18.7 (4.8)	19.2 (4.6)	19.1 (3.8)	18.5 (5.3)
Cognition score	18.2 (4.9)	18.5 (4.8)	19.4 (3.4)	18.2 (5.1)
Psychomotor function score	11.1 (4.9)	11.5 (4.4)	13.0 (4.3)	12.7 (4.8)
Motivation score	19.0 (5.0)	18.8 (5.0)	19.5 (3.2)	18.9 (4.9)
Sensory perception score	22.8 (5.4)	23.4 (5.6)	24.1 (4.1)	23.2 (5.9)

ITT, Intent-to-treat; MATHyS, Multidimensional Assessment of Thymic States.

All the values are presented in mean (SD).

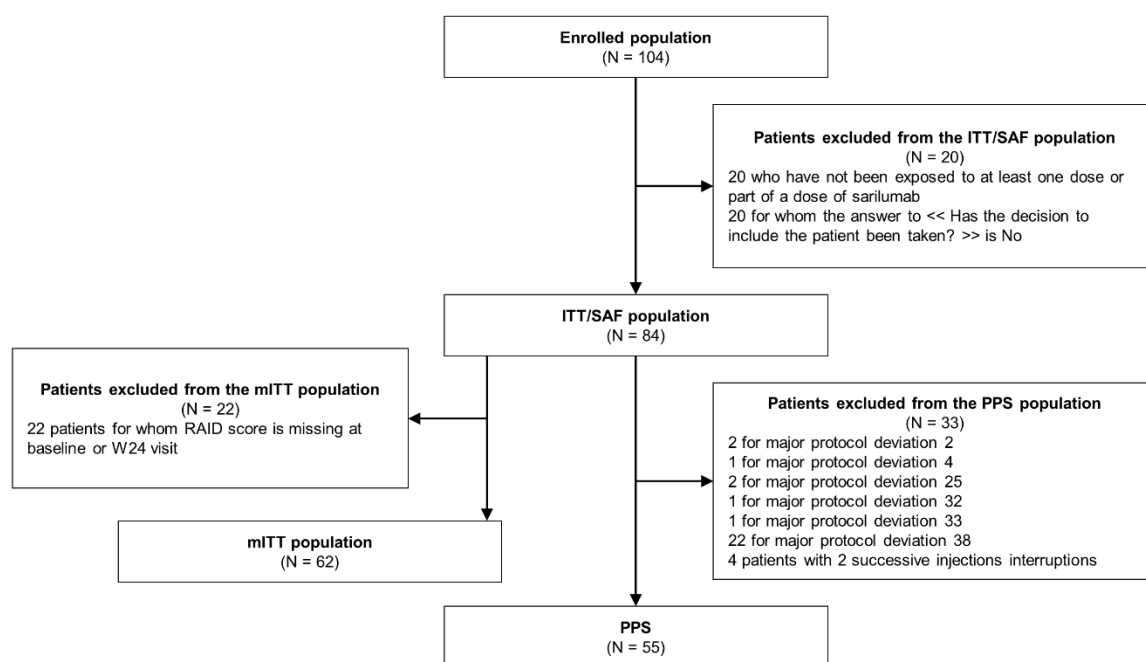
**Supplementary Fig. S1.** SariPRO study design



D, day; LTE, long-term extension; PT, post-treatment; q2w, every 2 weeks; SC, subcutaneous; W, week.

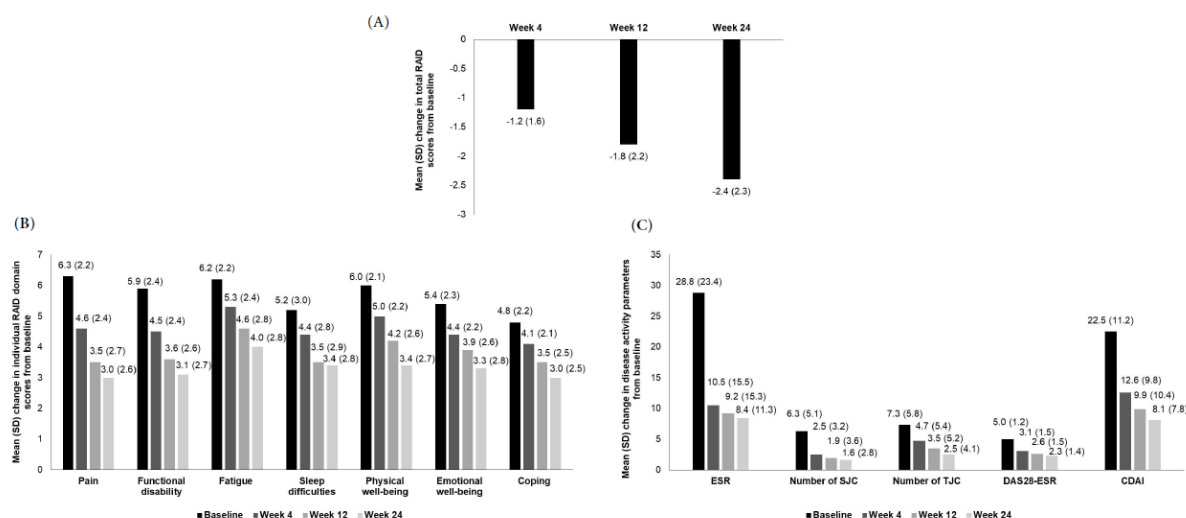
**Supplementary Fig. S2.** Patient disposition

## SariPRO Supplementary data



ITT, intent-to-treat; mITT, modified intent-to-treat; PPS, per protocol set; RAID, Rheumatoid Arthritis Impact of Disease; SAF, safety set; W, week.

**Supplementary Fig. S3. (A)** Change in the total RAID score, **(B)** Individual RAID domain scores, and **(C)** Disease activity parameters from baseline to week 24 ( $N = 84$ )



CDAI, clinical disease activity index; DAS, disease activity scores; ESR, erythrocyte sedimentation rate; RAID, rheumatoid arthritis impact of disease; SD, standard deviation; SJC, swollen joints count; TJC, tender joints count.