NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) STUDY REPORT

PASS information

Title	Non-Interventional Study to Review the Changes of Depression After First Year of Tofacitinib Treatment in Rheumatoid Arthritis (Xeljanz®)
Protocol number	A3921330
Version identifier of the study report	1.0
Date	09 DECEMBER 2024
EU Post Authorization Study (PAS) register number	EUPAS40263
Active substance	L04AA29 tofacitinib
Medicinal product	Xeljanz®
Product reference	EU/1/17/1178/003 SUKL code: 0222098
Procedure number	N/A
Marketing Authorization Holder (MAH)	[redacted]
Joint PASS	No
Research question and objectives	The primary objective of this study was to describe and evaluate the changes of depression level within 12 months from the start of tofacitinib therapy in patients with RA and at least minimal level of depression. The secondary objectives of this study were to describe and evaluate the level and changes of pain, anxiety, and insomnia in patients with rheumatoid arthritis (RA) and at least minimal level of depression. Also, the

[redacted]

	safety and effectiveness of tofacitinib for the treatment of RA is described.
Country(-ies) of study	Czech Republic
Author	[redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	[redacted]
MAH contact person	[redacted]

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1. ABSTRACT (STAND-ALONE DOCUMENT)

Stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
bDMARD	biological Disease Modifying Anti-Rheumatic Drug
bsDMARD	biosimilar Disease Modifying Anti-Rheumatic Drug
BMI	Body-mass index
CRP	C-Reactive Protein
CUDOS	Clinically Useful Depression Outcome Scale
CUXOS	Clinically Useful Anxiety Outcome Scale
e-CRF	Electronic case report form
ESR	erythrocyte sedimentation rate
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
GPP	Good Pharmacoepidemiology Practices
IEC	Independent Ethics Committee
INR	International normalized ratios
ISPE	International Society for Pharmacoepidemiology
JAK	Janus Kinase
JSEQ	Jenkins Sleep Evaluation Questionnaire
NIS	Non-interventional study
NSADR	Non-Serious Adverse Drug Reaction
NSAID	Non Steroidal Anti-Inflammatory Drug
PASS	Post-Authorization Safety study
RA	rheumatoid arthritis
SADR	Serious Adverse Drug Reaction
SAP	Statistical analysis plan
VAS	Visual Analogue Scale

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
[redacted]	Principal Investigator	[redacted]
[redacted]	Medical advisor	[redacted]
[redacted]	Medical Lead of Value Outcomes	[redacted]

Lead Country Investigator(s) of the Protocol

Not applicable.

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) approval of protocol. The IEC approval dates for the protocol and any amendments are provided in Appendix 3.2.	x	10 October 2019 28 January 2020	There were no IEC dates planned in the study protocol.
Start of data collection	01 June 2019	23 July 2020	
End of data collection	22 January 2024	07 February 2024	
Registration in the EU PAS register	30 April 2021	02 April 2021	
Final report of study results	21 December 2024	09 December 2024	

6. RATIONALE AND BACKGROUND

The rheumatoid arthritis (RA) is a is a chronic, inflammatory, autoimmune disease and its world-wide prevalence is 0.5-1.0% of the adult population (1).

The prevalence of psychological and psychiatric comorbidities (depression, anxiety, sleep disturbances) is increased in patients with rheumatoid arthritis similarly to other progressive rheumatologic diseases. E.g. a cross-sectional study carried out on 200 RA patients declares that the prevalence of depression, anxiety and disturbed sleep in their RA population was 23.5%, 27.5% and 44.5 % respectively (2). These conditions substantially influence the patient´s quality of life and therefore merit further investigation and better understanding. Several studies have investigated the prevalence of psychological comorbidities in RA patients, but the literature data revealing the influence of the novel biologic therapy on the occurrence or severity of these comorbidities are inadequate.

Patients with chronic pain often suffer from pain-related anxiety, overall affecting physical, social and emotional functioning of the patients (3). The high influence of psychological factors on quality of life in RA and psoriatic arthritis patients was revealed in study with 282 patients. The prevalence of moderate to severe levels of depressive symptoms was found in 25.1% RA patients (4).

The occurrence of depression, pain, anxiety, and sleep disturbances can be connected to RA. As expected, these comorbidities lead to the prescription of the analgesics (opioid, non-opioid, adjuvants), anxiolytics, antidepressants and/or hypnotics. Whether the use of JAK inhibitor (tofacitinib) in the treatment of the primary disease is associated with change in the prevalence or severity of these comorbidities is not well known. This prospective, observational, non-interventional study aimed to assess the changes in the level of depression in RA patients. This study enrolled patients with at least a minimal level of depression (by CUDOS scale), a sub-population of RA patients not sufficiently described in the previous trials, and the information is thus limited.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study was to describe and evaluate the changes of depression level within 12 months from the start of tofacitinib therapy in patients with RA and at least minimal level of depression. The primary goal was to find out if treatment by tofacitinib reduces depression by at least 10% within 12 months, based on the Clinically Useful Depression Outcome Scale (CUDOS) score (5).

The secondary objectives of this study were to describe and evaluate the level and changes of impact on patient´s life, anxiety (CUXOS questionnaire (6)), and insomnia (JSEQ questionnaire (7)) in patients with RA and at least minimal level of depression. Additionally, this study aimed to help in description of safety and effectiveness of tofacitinib for the treatment of RA.

7.1. Primary endpoint

The primary endpoint of the study:

- Relative change between visit 3 and baseline of CUDOS score.

7.2. Secondary endpoints

The secondary endpoints of the study:

- Baseline value and relative change between visit 2 and baseline of CUDOS score.
- Baseline value and relative change between Visit 2 and Visit 1 and between Visit 3 and Visit 1 of CUXOS, JSEQ and VAS score for evaluation of anxiety, insomnia, and arthritis assessment.
- Baseline counts of concomitant medication (antidepressants, analgesics, anxiolytics, and hypnotics) together with doses for each and the change in number of used medications and in their dosage between Visit 3 and Visit 1.
- Baseline value and absolute change between Visit 2 and Visit 1 and between Visit 3 and Visit 1 of DAS28-4.
- Remission as assessed by: DAS28-4 <2.6.
- LDA as assessed by: DAS284 <3.2.
- Change from Visit 1 in EuroQol Three Dimension – 3L (EQ-5D-3L) Health State Profile.
- Incidence of any adverse event (AE) reported by the patient or investigator.

8. AMENDMENTS AND UPDATES

Table 1 Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	18 June 2021	Substantial	6 Milestones	Milestones were updated.	The milestones were adjusted to reflect the current recruitment rate.
			7 Rational and background	Updated details of previous studies to align with current knowledge.	Updated information.
			8.1.2 Secondary endpoint	Added safety endpoints.	To align with PASS requirements.

Table 1 Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			9.2 Setting	Changed the definition of loss to follow-up. Enrollment months increased from 24 to 48 Clarified CUDOS score Updated study visit attendance and added further criteria for clarity	The definition was previously wrong and was now corrected.
			9.2.2 Exclusion criteria	Deleted criteria.	Patients will be prescribed study drug according to standard of care; therefore, some exclusion criteria were not required.
			9.3 Variables	Safety variables added.	The study meets criteria for being considered a PASS.
			9.3 Variables 9.4.1 Study procedures 9.4.1.2 Schedule of activities	Assessment of satisfaction with treatment will not be collected. Removed variable 'current RA treatment with tofacitinib' and eCRF where it was no longer applicable	Will not be relevant to the final data analysis.
			9.3 Variables 9.4.1 Study procedures 9.4.1.2 Schedule of activities	Physician global assessment will not be collected.	Will not be relevant to the final data analysis.
			9.4 Data source	Added details about data flow in CRF.	For clarification.
			9.4.3 Assessments – Efficacy	Updated patient assessments. Clarification that CRP and ESR are not required per protocol and that disease activity indicator (DAS 28) is evaluated as standard of care assessment.	For clarification.

Table 1 Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			9.4.4.1 Safety Criteria	Section was updated to contain more clarity.	For clarification.
			9.6 Data Management	Process of Patient reported outcome (PRO) completion and processing updated.	For clarification.
			9.7.2 Efficacy analysis	Deleted details about EQ-5D-3L PRO.	These details will be documented in the SAP and are not required in the protocol.
			9.7.4 Interim analysis	Details regarding Statistical Analysis Plan were added.	Clarification where methodology of statistical analysis can be found.
			9.8 Quality control	Data review and data cleaning processes were added.	Details on how data will be reviewed and cleaned were missing and were added.
			10.5 Ethical conduct of the study	Not applicable requirements were deleted and only local and study specific requirements were kept.	This section was adapted to the study type and the location. Only applicable requirements were kept in this paragraph.
			11.1 Safety requirements (Table 9)	Added the list of AEs to be reported to the sponsor.	These changes were made to align with the processes of the sponsor.
			Section 12	Updated submission timeline to SUKL from 150 days to 12 months.	To align with internal timelines.
			Throughout the protocol	Change the time window for the 12 months visit from ±30 days to ±45 days for V3. Minor editorial updates throughout	This change was decided to allow more flexibility.

9. RESEARCH METHODS

9.1. Study design

This was a single arm, prospective cohort non-interventional, multi-center study according to Czech legal definitions (Law 378/2007 Sb.).

For the description and evaluation of depression level and its changes in RA patients the prospective data from a 12-month follow-up were collected. The depression assessment was performed by using the CUDOS questionnaire in the form of a printed patient questionnaire presented to patients on each study visit and transcribed to an anonymous electronic case report form (eCRF).

For the description and evaluation of arthritis, anxiety, and insomnia in RA patients with at least minimal depression (as per CUDOS questionnaire) the prospective data from a 12-month follow-up was used. The patient assessment of arthritis, anxiety and insomnia was performed by using the 100 mm VAS scale, CUXOS and JSEQ questionnaires, respectively, in form of a printed patient questionnaire presented to patients on each study visit.

The study followed one cohort of patients who were newly prescribed tofacitinib at Visit 1 and who scored at least 11 points on CUDOS scale (equivalent of minimal depression).

There were 3 visits planned for each patient:

- Visit 1 (start of tofacitinib treatment).
- Visit 2 (6 months after start of tofacitinib treatment).
- Visit 3 (12 months after start of tofacitinib treatment).

This non-interventional study did not impose any additional procedures, assessments or changes to the routine management of patients treated with tofacitinib, which was prescribed in the usual manner in accordance with the terms of the marketing authorization. Data were obtained from medical records and patient questionnaires and transcribed to a pseudonymous electronic case report form (e-CRF).

All patients were required to sign the written inform consent, incl. consent to the use of personal data.

9.2. Setting

This non-interventional study followed the population of 70 patients with moderate to severe rheumatoid arthritis, who were currently prescribed tofacitinib treatment for the first time and who scored at least 11 points on CUDOS scale (equivalent of minimal depression).

Patients were followed for the period of 12 months and had a total of 3 visits per patient as per common medical care.

The data were collected by physicians allowed (according to indication restriction of reimbursement) to prescribe tofacitinib and, at the same time, were specialized in the treatment of rheumatoid arthritis – rheumatologists. A total number of 6 study sites were involved.

Requirements for the physician´s eligibility are as followed: out-patient setting of the clinical practice, satisfactory experience in the care of patients with rheumatological diseases, and sufficient number of patients with diagnosis of rheumatoid arthritis.

Study flow:

- Patient signed informed consent.
- Evaluation of inclusion/exclusion criteria.
- Patient enrollment.
- Visit 1 (Baseline visit) (start of tofacitinib treatment).
  - eCRF completion.
  - Completion of printed patient questionnaires.
- Visit 2 (6 months ±30 days after start of tofacitinib treatment):
  - AE detection, processing, and reporting, if applicable.
  - eCRF completion.
  - Completion of printed patient questionnaires.
- Visit 3 (12 months ±45 days after start of tofacitinib treatment):
  - AE detection, processing, and reporting, if applicable.
  - eCRF completion.
  - Completion of printed patient questionnaires.

Subjects could be discontinued for the following reasons:

- The switch to a different treatment (for any reason – e.g. new contraindication as per Summary of Product Characteristics (SmPC), tofacitinib interaction with other medicine, adverse reactions).
- Non-compliance with the study schedule – the patient not coming for the planned study visit (which by the non-interventional setting of the study had to be planned for the same date as the visit planned within normal clinical practice). The period for study visits attendance was ±30 days for V2 and ±45 days for V3.

It was expected (based on the clinic's experience) for the patients to be enrolled within 48 months from the start of the study – the enrollment of new subjects was closed after 30 months.

9.3. Subjects

9.3.1. Inclusion Criteria

Patients had to meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients aged ≥18 years.

2. Moderate to severe activity of rheumatoid arthritis (DAS28 ≥3.2).

3. Patient for whom the physician decision had been made to initiate a treatment with tofacitinib.

4. Patient with at least minimal level of depression (CUDOS questionnaire ≥11 points).

5. Capable of understanding and signing a written informed consent form.

6. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

9.3.2. Exclusion Criteria

Patients meeting any of the following criteria were not included in the study:

1. Patients unwilling/unable to fill in printed patient questionnaires.

9.4. Variables

Table 2 Study variables

Variable	Role	Data Source(s)	Operational Definition
RA treatment with tofacitinib – date of initiation	Exposure, Potential confounder, subgroup identifier	Medical records	For details, see SAP
RA treatment with tofacitinib – dose	Exposure, Potential confounder, subgroup identifier	Medical records	For details, see SAP
RA treatment with tofacitinib - tolerability	Potential confounder, subgroup identifier	Medical records	For details, see SAP
Age	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Gender	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Height	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Weight	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Smoking history and current smoking status	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Alcohol intake	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Date of first diagnosis of RA	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP
Co-morbidities	Visit 1 characteristic, potential confounder, sub-group identifier	Medical records	For details, see SAP

Table 2 Study variables

Variable	Role	Data Source(s)	Operational Definition
Prior pharmacotherapy for RA	Potential confounder, sub-group identifier	Medical records	For details, see SAP
Co-medication relevant to RA and mental health	Potential confounder, sub-group identifier	Medical records	For details, see SAP
Patient Assessment of Depression (CUDOS) (5)	Visit 1 and Outcome	Printed questionnaire	For details, see SAP
Patient Assessment of Arthritis	Visit 1 and Outcome	Printed questionnaire	For details, see SAP
Patient Assessment of Anxiety (CUXOS) (6)	Visit 1 and Outcome	Printed questionnaire	For details, see SAP
Patient Assessment of Insomnia (JSEQ) (7)	Visit 1 and Outcome	Printed questionnaire	For details, see SAP
Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP)	Visit 1 and Outcome	Medical records	For details, see SAP
DAS28-4	Visit 1 and Outcome	Medical records	For details, see SAP
EuroQol EQ-5D-3L Health State Profile	Visit 1 and Outcome	Printed questionnaire	For details, see SAP
Occurrence of adverse events	Outcome	Medical records	For details, see SAP

9.5. Data sources and measurement

The data were obtained from medical records and patient questionnaires, this study did not impose any additional procedures, assessments or changes to the routine management of patients. The data were transcribed to a pseudonymous e-CRF.

9.6. Bias

The study was susceptible to selection bias. Patients who choose to participate in studies are more likely to exhibit different characteristics (such as healthier habits, less concomitant diseases) than non-participants (8). Another source of bias could be information bias due to misclassification concerning adverse events. Furthermore, as with any “as observed” analysis, there was a potential risk of bias due to missing outcome data; the risk increases with increasing number of missing outcome data.

9.7. Study Size

The sample size was determined based on the primary endpoint which describes the change of the CUDOS score after 12 months of tofacitinib treatment – assessing the change in depression after the 12-month treatment. The sample size was computed to detect the reduction of score by 10%, which was expected by current research articles.

The sample size was calculated for paired t-test of logarithm of CUDOS score with 5% alpha level, power 90% and two-sided alternative. For the calculation, it was assumed that the score would be reduced by 10% after the therapy. Standard deviation was based on assumption that mean Visit 1 score is 27.9 with standard deviation 9.9 and decreases by 10% to mean value score 25.1 keeping the same standard deviation 9.9 after the therapy. The correlation between the second and first measurement was expected to be 0.5, which was based on expert opinion.

The study aimed to enrol 154 patients. After an expected 20% drop out rate, 123 remaining patients could be analysed.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g. many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 4).

9.9. Statistical methods

9.9.1. Main summary measures

Categorical outcomes were summarized by the number and percentage in each category.

Continuous outcomes were summarized by mean, standard deviation, median, interquartile range, minimum and maximum values.

9.9.2. Main statistical methods

All data collected within this study were assessed and presented using descriptive statistics and, if appropriate, illustrated graphically. R-Software (Version 4.4.0) was used for all analyses.

For the primary analysis (determination of the changes in CUDOS score) a paired t-test comparing CUDOS scores at Visit 1 with those obtained at the follow-up Visit 3 after 12 months was conducted. The specific null hypothesis was that the difference between scores after and before therapy equals 0, as opposed to the alternative hypothesis, which suggested a difference in scores after and before treatment. The null hypothesis was tested at a significance level of alpha = 0.05.

As a secondary hypothesis, we investigated whether the effect of treatment on decrease of CUDOS score was already present after 6 months (Visit 2), considering the primary analysis showed a significant decrease of CUDOS score after 12 months (Visit 3).

Other secondary hypotheses were that anxiety, insomnia, and arthritis assessments would improve in patients treated with tofacitinib, indicating that CUXOS, JSEQ, and VAS scores would decrease after treatment. Initially, the decrease after 12 months of treatment was tested. Since a significant change in scores was observed in all three cases, the same hypotheses were tested after 6 months of treatment. As with the primary and first secondary analyses, paired t-tests on the original metrics of scores were employed instead of ratio t-tests due to the presence of zero values in scores after treatment. However, similar to previous cases, this method remains appropriate for the data, and the results remain valid. The null hypotheses were the same as in the primary analysis: the difference between the score after and before therapy equals 0, against the alternative that a difference in scores after and before treatment exists.

The number and percentage of patients with concomitant medication before and after the treatment were assessed and presented using descriptive statistics (separately for methotrexate, analgesics, antidepressants, anxiolytics, and hypnotics).To assess the first secondary exploratory analysis, we used a model that employs a hierarchical structural

equation approach to test the mediation of changes in depression by changes in disease activity, with the impact of arthritis as an additional mediator. This hierarchical structure allows for the examination of both direct and indirect pathways influencing depression outcomes over time. In this analysis, the primary focus lies on understanding two key metrics: the standardized error coefficient for CUDOS and the path coefficient representing the relationship between CUDOS and change in DAS28. The standardized error coefficient (also known as the residual variance) for CUDOS gives us the proportion of variance in CUDOS that is not explained by the predictors in the model (Visit 1 CUDOS, change in DAS28, and VAS). This can be interpreted as the extent to which factors other than those included in the model influence depression.

To assess the second secondary exploratory analysis, the linear mixed-effects model was employed to account for the hierarchical structure of the data, with repeated measures on patients across different visits. The model included the EQ-5D utility score as the dependent variable and CUDOS, CUXOS, JSEQ and VAS scores as fixed effects, with a random intercept for each patient to capture individual variability. The model was fitted using Restricted Maximum Likelihood (REML) estimation.

9.9.3. Missing values

Completeness and quality of data recorded in the eCRF were monitored by Data Manager. Missing or inconsistent data were communicated to the study site. Due to the non-interventional nature of the study, the extent of data cleansing was limited.
Unused or inconsistent data were classified with missing data together as ‘incorrect or missing data’. The number of incorrect or missing data is part of all outcomes from descriptive analysis.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None

9.10. Quality control

Data entry into e-CRF was performed by qualified trained subjects only. Entered data were reviewed for consistency and logic via implemented quality checks and by manual reviews, as well. Remote as well as on-site monitoring approach was applied throughout the conduction of this study.

9.11. Protection of human subjects

Subject information and consent

Written informed consent (Appendix 6) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Independent Ethics Committee (IEC)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by IEC(s) for each site participating in the study.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

10. RESULTS

10.1. Participants

A total of 73 patients were enrolled in the study (signed an Informed consent form). Data analysis included 70 patients at Visit 1, 66 patients at Visit 2 and 62 patients at Visit 3. Of 62 patients that completed the Visit 3, no patients had to be excluded from the analysis based on exclusion criteria during final analysis.

Table 3 Number of patients

	Number of patients
Enrolled*	**73**
Completed	62
Discontinued	11
Analysed**	**70**
Visit 1	70
Visit 2	66
Visit 3	62

* signed Informed consent form
** patients who received at least one dose of study medication

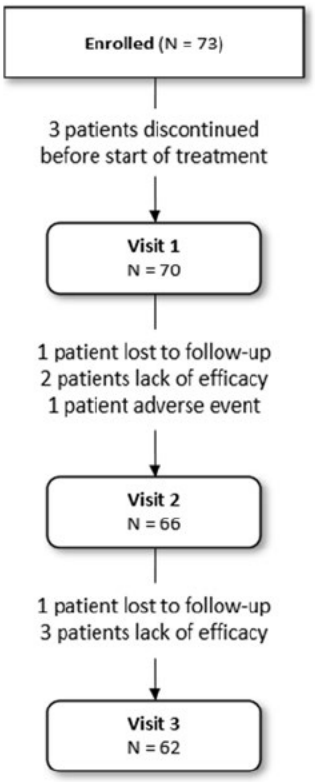


Figure 1 Patient flow

Table 4 Discontinuations from the study

	N=73	%
Discontinued	**11**	**15.1%**
Discontinued not treated	3	4.1%
Discontinued treated	8	11.0%
Relation to study drug not defined	6	8.2%
Related to study drug	2	2.7%
Not related to study drug	3	4.1%
Lost to follow-up	5	6.8%
Adverse event	1	1.4%
Lack of efficacy	5	6.8%
Before start of treatment	3	4.1%
Between V1 and V2	4	5.5%
Between V2 and V3	4	5.5%

10.2. Descriptive data

All the in-text descriptive data are based on the FAS population, defined as patients who receive at least one dose of tofacitinib and have the data for evaluation of primary hypothesis, which means CUDOS reported both at Visit 1 and Visit 3, as originally planned in SAP.

10.2.1. Demographic characteristics

Overall, 53 (85.5%) patients were female. The mean age (±SD) of the study population was 58.1 (±13.31) years, the youngest patient was 25 years old, and the oldest patient was 77 years old. The mean patient BMI at Visit 1 was 26.6 (±4.93) kg/m^2. For demographic characteristics of all patients (Safety population), see Section 15.

A total of 14 (22.6%) patients were smokers. Of 62 patients, 12 patients consumed at least 1 unit of alcohol per week. Alcohol consumers mostly consumed 1 alcohol unit per week, 1.67 units on average.

Table 5 Demographic characteristics

	N	% / Mean	SD	Median	IQR	Min	Max
Sex							
Female	53	85.5%					
Male	9	14.5%					
Age* [years]	62	58.06	13.31	60.0	18.3	25.0	77.0
Body height [cm]	62	170.13	8.08	169.5	5.0	150.0	198.0
Body weight [kg]	62	77.09	16.03	75.5	24.8	53.0	118.0
BMI [kg/m2]	62	26.59	4.93	26.4	7.8	18.8	41.3
Smoking status							
No	48	77.4%					

Table 5 Demographic characteristics

	N	% / Mean	SD	Median	IQR	Min	Max
Yes**	14	22.6%					
Alcohol intake							
No	50	80.6%					
Yes	12	19.4%					
Alcohol intake [units*/week]**	12	1.67	0.89	1.0	1.3	1.0	3.0

**at Visit 1*
***at least one cigarette a day*
****one unit is equal to 2 dcl of wine or 0.5 l of beer or 50 ml of hard liquor*

10.2.2. Disease characteristics

At Visit 1, the average time since the RA diagnosis was 13.57 (± 9.02) years.

Table 6 Time since RA diagnosis

	N	Mean	SD	Median	IQR	Min	Max
Time since RA diagnosis* [years]	62	13.57	9.02	10.74	11.14	1.02	35.84

At Visit 1 the disease activity was assessed. The mean (SD) disease activity (using DAS28-4 score) was 5.86 (0.85).

10.2.3. RA comorbidities

In total, there were 43 (69.4%) patients reported as having at least 1 comorbidity in addition to RA. The most common comorbidities belonged to the group of metabolic/endocrine, cardiovascular, musculoskeletal disorders affecting 40.3%, 38.7%, 30.6% patients, respectively. A detailed overview of all observed comorbidities is provided in Section 15.

Table 7 Comorbidities

	N	%
Comorbidities		
0 comorbidities	19	30.6%
1-2 comorbidities	29	46.8%
3 or more comorbidities	14	22.6%
Metabolic/endocrine disorders	25	40.3%
Cardiovascular diseases	24	38.7%
Musculoskeletal disorders	19	30.6%
Gastrointestinal diseases	9	14.5%
Psychiatric disorders	6	9.7%
Urological/renal diseases	5	8.1%
Other diseases	5	8.1%
Pulmonary diseases	2	3.2%
Malignancies	0	0.0%

10.2.4. Treatment preceding tofacitinib

At Visit 1 all the previous medication used for the RA treatment was reported. In average, within the period from the start of RA treatment until the start of tofacitinib treatment, the patients were prescribed 2.63 synthetic systemic medicinal products. The most common systemic active substances were methotrexate and leflunomide, used by 59 (95.2%) and 29 (46.8%) patients, respectively.

Table 8 Treatment preceding tofacitinib - Synthetic systemic medication

	N	%
Synthetic systemic medication		
Methotrexate	59	95.2%
Leflunomide	29	46.8%
Sulfasalazine	20	32.3%
Systemic glucocorticoids	20	32.3%
NSAIDs	19	30.6%
Hydroxychloroquine	8	12.9%
Gold salts	6	9.7%
Azathioprine	1	1.6%
Chloroquine	1	1.6%

Table 9 Number of previously used synthetic systemic medication

	N	%
Number of previously used synthetic systemic medication		
1-2 systemic medications	34	54.8%
3 or more systemic medications	28	45.2%

In total, 26 (41.9%) and 26 (41.9%) patients were in the past treated with intra-articular corticosteroids and topical NSAIDs, respectively.

In average, during the period from the start of RA treatment until the start of tofacitinib treatment, the patients were prescribed 1.34 biologic medicinal products. The most common biologicals were etanercept and adalimumab, used by 22 (35.5%) and 19 (30.6%) patients, respectively.

For most of the patients who previously used any biological (74.4%), the reason to end the biological treatment and start tofacitinib, was insufficient efficiency. Other reasons were e.g. adverse events or the end of participation in a clinical trial.

Table 10 Treatment preceding tofacitinib - Biologicals

	N	%
Biologicals (bDMARDs or bsDMARDs)	43	69.4%
Etanercept	22	35.5%
Adalimumab	19	30.6%
Infliximab	6	9.7%
Tocilizumab	6	9.7%
Golimumab	5	8.1%
Abatacept	4	6.5%
Certolizumab	4	6.5%
Sarilumab	4	6.5%
Baricitinib	3	4.8%
Rituximab	3	4.8%
Other	7	11.3%

Table 11 Number of previously used biologicals

	N	%
Number of previously used biologicals		
0 biologicals	19	30.6%
1-2 biologicals	34	54.8%
3 or more biologicals	9	14.5%

10.2.5. Tofacitinib treatment

The table below describes tofacitinib doses prescribed to the RA patients (FAS population). For the doses prescribed to patients treated with tofacitinib but discontinued from the study for any reason (N=8), see Section 15.

Table 12 Tofacitinib dosing

	Total	Tofacitinib dose					
		11 mg/once a day		5 mg once a day		5 mg/twice a day	
		N	%	N	%	N	%
Visit 1	62	20	32.3%	0	0.0%	42	67.7%
Visit 2	62	19	30.6%	0	0.0%	43	69.4%
Visit 3	62	20	32.3%	0	0.0%	42	67.7%

10.3. Outcome data

FAS population

- defined as patients who receive at least one dose of tofacitinib and have the data for evaluation of primary hypothesis, which means CUDOS reported both at Visit 1 and Visit 3.

- used in Section 10.2, Section 10.4.1, Section 10.4.2, Section 10.5.

Safety population

- defined as all patients who receive at least one dose of tofacitinib. This population was used for all safety analyses.
- used in Section 10.6.

10.4. Main results

10.4.1. Primary endpoint

10.4.1.1. Relative change of CUDOS score between Visit 3 and Visit 1

The primary objective of this study was to describe and evaluate changes in depression levels after 12 months after the initiation of tofacitinib treatment in patients with RA who exhibited at least a minimal level of depression. Our primary hypothesis was that depression would improve in treated patients, indicating a decrease in CUDOS scores after 12 months of tofacitinib treatment. This hypothesis was initially tested with a ratio t-test (paired test logarithm). CUDOS scores after therapy also contained zero values, and therefore the logarithm of the ratio is not defined in this case and the ratio t-test could not be used.

Instead, the paired t-test was used as an alternative test listed in the statistical analysis plan.

The results indicate statistically significant difference between the CUDOS scores measured before and after 12-month tofacitinib treatment, with a p-value < 0.001. Hence, we reject the null hypothesis and conclude that there was a statistically significant decrease in CUDOS scores after tofacitinib treatment.

The mean change in CUDOS score after 12 months of tofacitinib treatment is a decrease by 12.68 points, i.e. by 53.1%.

Table 13 Mean difference in CUDOS scores before and after the 12-month tofacitinib treatment

N	CUDOS at Visit 1		CUDOS at Visit 3		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
62	21.97	9.45	9.29	6.71	12.68	< 0.001	(9.96 ; 15.39)

The mean relative change of CUDOS score between Visit 1 and Visit 3 is a decrease by 53.1%.

In total, between Visit 1 and Visit 3, CUDOS score decreased in 59 out of 62 patients (95.2%) who completed the 12-month follow-up. The increase of CUDOS score (in the range of 10-30%) was observed in 3 out of 62 patients (4.8%) There was no patient whose CUDOS score wouldn´t change at all.

Table 14 Changes of CUDOS score after 12-month tofacitinib treatment

	N	%
Total	62	100.0%
Decrease of CUDOS score between Visit 1 and Visit 3	59	95.2%
< 10%	2	3.2%
10% - 30%	7	11.3%
30% - 50%	17	27.4%
50% - 70%	9	14.5%
> 70%	24	38.7%
Increase of CUDOS score between Visit 1 and Visit 3	3	4.8%
< 10%	0	0.0%
10% - 30%	3	4.8%
30% - 50%	0	0.0%
50% - 70%	0	0.0%
> 70%	0	0.0%
No change of CUDOS score between Visit 1 and Visit 3	0	0.0%

10.4.2. Secondary endpoints

10.4.2.1. Relative change of CUDOS score between Visit 2 and Visit 1

As a secondary hypothesis, we investigated whether the effect of tofacitinib treatment on decrease of CUDOS score was already present after 6 months (Visit 2), considering the primary analysis showed a significant decrease of CUDOS score after 12 months of tofacitinib treatment.

The results of the paired t-test indicate that there was a significant difference in CUDOS scores between Visit 1 and Visit 2 (p-value < 0.001). Thus, we can conclude that the effect of the treatment was already observed 6 months after the start of tofacitinib treatment.

The mean change of CUDOS score after 6 months of tofacitinib treatment is a decrease by 9.18 points, i.e. by 35.4%.

Table 15 Mean difference in CUDOS scores before and after the 6-month tofacitinib treatment

N	CUDOS at Visit 1		CUDOS at Visit 2		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
62	21.97	9.45	12.79	8.71	9.18	< 0.001	(6.39 ; 11.97)

The mean relative change of CUDOS score between Visit 1 and Visit 2 is a decrease by 35.4%.

In total, between Visit 1 and Visit 2, CUDOS score decreased in 54 out of 62 patients (87.1%). The increase of CUDOS score was observed in 8 out of 62 patients (12.9%) There was no patient whose CUDOS score wouldn´t change at all.

Table 16 Changes of CUDOS score after 6-month tofacitinib treatment

	N	%
Total	62	100.0%
Decrease of CUDOS score between Visit 1 and Visit 2	54	87.1%
< 10%	5	8.1%
10% - 30%	10	16.1%
30% - 50%	14	22.6%
50% - 70%	13	21.0%
> 70%	12	19.4%
Increase of CUDOS score between Visit 1 and Visit 2	8	12.9%
< 10%	3	4.8%
10% - 30%	0	0.0%
30% - 50%	1	1.6%
50% - 70%	0	0.0%
> 70%	4	6.5%
No change of CUDOS score between Visit 1 and Visit 2	0	0.0%

10.4.2.2. Relative change of CUXOS (anxiety) score between Visit 3 and Visit 1

The results of the paired t-test indicate a statistically significant difference between the CUXOS scores measured before and after 12 months of tofacitinib treatment, since a p-value was lower than 0.001. Hence, we reject the null hypothesis and conclude that there was a statistically significant decrease in CUXOS scores after treatment.

The mean change in CUXOS score between Visit 1 and Visit 3 is a decrease by 12.24 points, i.e. by 47.1%.

Table 17 Mean difference in CUXOS scores before and after the 12-month tofacitinib treatment

N	CUXOS at Visit 1		CUXOS at Visit 3		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
62	20.45	14.21	8.21	8.66	12.24	< 0.001	(8.81; 15.67)

Table 18 Changes of CUXOS score after 12-month tofacitinib treatment

	N	%
Total	62	100.0%
Decrease of CUXOS score between Visit 1 and Visit 3	52	83.9%
< 10%	2	3.2%
10% - 30%	4	6.5%
30% - 50%	10	16.1%
50% - 70%	11	17.7%
> 70%	25	40.3%
Increase of CUXOS score between Visit 1 and Visit 3	6	9.7%
< 10%	0	0.0%
10% - 30%	3	4.8%
30% - 50%	0	0.0%
50% - 70%	1	1.6%
> 70%	2	3.2%
No change of CUXOS score between Visit 1 and Visit 3	4	6.5%

10.4.2.3. Relative change of CUXOS (anxiety) score between Visit 2 and Visit 1

Considering the difference in CUXOS scores between Visit 1 and Visit 3 after 12 months of treatment was significant, we also tested the difference in scores between Visit 1 and Visit 2 (after 6 months of treatment). Since the p-value of the paired t-test resulted in less than 0.001, we can reject the null hypothesis and conclude that the difference in CUXOS scores was already significant after 6 months of treatment.

The mean difference in CUXOS scores between Visit 1 and Visit 2 is a decrease by 8.21 points, i.e. by 33.2%.

Table 19 Mean difference in CUXOS scores before and after the 6-month tofacitinib treatment

N	CUXOS at Visit 1		CUXOS at Visit 2		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
62	20.45	14.21	12.24	11.31	8.21	< 0.001	(5.02; 11.40)

Table 20 Changes of CUXOS score after 6-month tofacitinib treatment

	N	%
Total	62	100.0%
Decrease of CUXOS score between Visit 1 and Visit 2	52	83.9%
< 10%	3	4.8%
10% - 30%	9	14.5%
30% - 50%	11	17.7%
50% - 70%	13	21.0%
> 70%	16	25.8%
Increase of CUXOS score between Visit 1 and Visit 2	7	11.3%
< 10%	1	1.6%
10% - 30%	2	3.2%
30% - 50%	0	0.0%
50% - 70%	2	3.2%
> 70%	2	3.2%
No change of CUXOS score between Visit 1 and Visit 2	3	4.8%

10.4.2.4. Relative change of JSEQ (insomnia) score between Visit 3 and Visit 1

The level of insomnia and sleep disturbance was measured using JSEQ questionnaire. By testing the difference in JSEQ scores between Visit 1 and Visit 3 (after 12 months of treatment), we rejected the null hypothesis about no difference between them and can thus conclude that there is a significant difference between the scores based on the paired t-test.

On average, between Visit 1 and Visit 3 the JSEQ score decreased by 3.92 points, i.e. by 34.5%.

Table 21 Mean difference in JSEQ scores before and after the 12-month tofacitinib treatment

N	JSEQ at Visit 1		JSEQ at Visit 3		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
62	9.40	4.78	5.48	3.52	3.92	< 0.001	(2.73; 5.11)

Table 22 Changes of JSEQ score after 12-month tofacitinib treatment

	N	%
Total	62	100.0%
Decrease of JSEQ score between Visit 1 and Visit 3	48	77.4%
< 10%	2	3.2%
10% - 30%	8	12.9%
30% - 50%	10	16.1%
50% - 70%	17	27.4%
> 70%	11	17.7%
Increase of JSEQ score between Visit 1 and Visit 3	11	17.7%
< 10%	0	0.0%
10% - 30%	4	6.5%
30% - 50%	2	3.2%
50% - 70%	1	1.6%
> 70%	4	6.5%
No change of JSEQ score between Visit 1 and Visit 3	3	4.8%

10.4.2.5. Relative change of JSEQ (insomnia) score between Visit 2 and Visit 1

As a subsequent hypothesis, the difference in JSEQ score between Visit 1 and Visit 2 was tested. The results of the paired t-test showed a p-value of less than 0.001 indicating that there is a significant difference between the scores.

The mean difference in JSEQ scores between Visit 1 and Visit 2 is a decrease by 2.77 points, i.e. by 27.6%.

Table 23 Mean difference in JSEQ scores before and after the 6-month tofacitinib treatment

N	JSEQ at Visit 1		JSEQ at Visit 2		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
62	9.40	4.78	6.63	4.61	2.77	< 0.001	(1.59; 3.96)

Table 24 Changes of JSEQ score after 6-month tofacitinib treatment

	N	%
Total	62	100.0%
Decrease of JSEQ score between Visit 1 and Visit 2	45	72.6%
< 10%	1	1.6%
10% - 30%	10	16.1%
30% - 50%	14	22.6%
50% - 70%	11	17.7%
> 70%	9	14.5%
Increase of JSEQ score between Visit 1 and Visit 2	11	17.7%
< 10%	1	1.6%
10% - 30%	3	4.8%
30% - 50%	1	1.6%
50% - 70%	3	4.8%
> 70%	3	4.8%
No change of JSEQ score between Visit 1 and Visit 2	6	9.7%

10.4.2.6. Relative change of VAS (arthritis assessment) score between Visit 3 and Visit 1

The level of arthritis impact on patients' lives was assessed using the 100 mm VAS scale, where patients marked how much arthritis affected their lives on a scale of 0 (no impact) to 100 (maximum impact). Because the question was added to the eCRF later in the study, only 38 patients from the complete FAS set provided answers. As in previous cases, the difference in VAS scores between Visit 1 and Visit 3 (after 12 months of treatment) was first tested using the paired t-test. The results revealed a statistically significant difference between the scores measured before and after treatment, with a p-value < 0.001. Hence, we reject the null

hypothesis and conclude that there was a statistically significant decrease in VAS scores after the 12-month treatment.

The mean difference in VAS scores between Visit 1 and Visit 3 is a decrease by 27.55 points, i.e. by 35.4%.

Table 25 Mean difference in VAS scores before and after the 12-month tofacitinib treatment

N	VAS at Visit 1		VAS at Visit 3		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
38	61.42	18.62	33.75	26.57	27.55	< 0.001	(16.14; 38.97)

Table 26 Changes of VAS score after 12-month tofacitinib treatment

	N	%
Total	38	100.0%
Decrease of VAS score between Visit 1 and Visit 3	29	76.3%
< 10%	1	2.6%
10% - 30%	3	7.9%
30% - 50%	3	7.9%
50% - 70%	5	13.2%
> 70%	17	44.7%
Increase of VAS score between Visit 1 and Visit 3	9	23.7%
< 10%	1	2.6%
10% - 30%	4	10.5%
30% - 50%	1	2.6%
50% - 70%	0	0.0%
> 70%	3	7.9%
No change of VAS between Visit 1 and Visit 3	0	0.0%

10.4.2.7. Relative change of VAS (arthritis assessment) score between Visit 2 and Visit 1

The difference in VAS scores between Visit 1 and Visit 2 was tested, considering there was a significant difference observed in scores between Visit 1 and Visit 3 (after 12 months of treatment). The test results showed a significant difference in the VAS score between Visit 1

and Visit 2 (p-value < 0.001). Thus, we can conclude that the effect of the treatment on VAS scores was already present 6 months after the start of tofacitinib treatment.

On average, VAS score at Visit 2 was approximately 29.58 points lower than the score at Visit 1. The average percentage decrease in score was about 43.4%.

Table 27 Mean difference in VAS scores before and after the 6-month tofacitinib treatment

N	VAS at Visit 1		VAS at Visit 2		Mean difference	p-value	95% CI
	mean	SD	mean	SD			
38	61.42	18.62	33.58	20.34	29.58	< 0.001	(21.32; 37.84)

Table 28 Changes of VAS score after 6-month tofacitinib treatment

	N	%
Total	38	100.0%
Decrease of VAS score between Visit 1 and Visit 2	34	89.5%
< 10%	1	2.6%
10% - 30%	5	13.2%
30% - 50%	9	23.7%
50% - 70%	10	26.3%
> 70%	9	23.7%
Increase of VAS score between Visit 1 and Visit 2	4	10.5%
< 10%	0	0.0%
10% - 30%	0	0.0%
30% - 50%	3	7.9%
50% - 70%	1	2.6%
> 70%	0	0.0%
No change of VAS between Visit 1 and Visit 2	0	0.0%

10.4.2.8. Counts and dose of concomitant medication, changes between Visit 3 and Visit 1

The most common medication used for RA treatment (besides tofacitinib) was methotrexate (61.3%), analgesics (56.5%) and systemic glucocorticoids (54.8%).

Table 29 Concomitant RA treatment per study visit

Concomitant RA treatment (N=62)	Visit 1		Visit 2		Visit 3	
	N	%	N	%	N	%
Methotrexate	38	61.3%	32	51.6%	31	50.0%
Analgesics	35	56.5%	17	27.4%	14	22.6%
Systemic NSAIDs (coxibs)	4	6.5%	3	4.8%	4	6.5%
Systemic NSAIDs (other than coxibs)	23	37.1%	9	14.5%	5	8.1%
Tramadol	4	6.5%	2	3.2%	4	6.5%
Paracetamol	8	12.9%	5	8.1%	4	6.5%
Other	2	3.2%	2	3.2%	0	0.0%
Other systemic RA treatment (besides tofacitinib, methotrexate and analgesics)	34	54.8%	27	43.5%	35	56.5%
Systemic glucocorticoids	34	54.8%	24	38.7%	31	50.0%
Leflunomide	6	9.7%	4	6.5%	5	8.1%
Hydroxychloroquine	2	3.2%	1	1.6%	1	1.6%
Locally applied forms of RA treatment	2	3.2%	1	1.6%	1	1.6%
Topical NSAIDs	2	3.2%	1	1.6%	1	1.6%
Intra-articular glucocorticoids	1	1.6%	0	0.0%	0	0.0%

*The table displays an overview of all medicines with an occurrence in at least one patient.

In total, 38 out of 62 patients (61.3%) used methotrexate as a concomitant medication to tofacitinib at Visit 1. During the 12-month follow-up 9 patients stopped using methotrexate and 2 patients initiated the MTX treatment.

The most common RA concomitant combination to tofacitinib was a triple-combination of methotrexate and analgesics and systemic glucocorticoids (21.0%). The second most common combination was methotrexate and analgesics (19.4%).

Table 30 Combinations of RA tofacitinib-concomitant treatment

	Visit 1		Visit 2		Visit 3	
	N	%	N	%	N	%
Methotrexate only	5	8.1%	15	24.2%	14	22.6%
Methotrexate + Analgesics	12	19.4%	5	8.1%	5	8.1%
Methotrexate + Systemic glucocorticoids	13	21.0%	9	14.5%	10	16.1%

Table 30 Combinations of RA tofacitinib-concomitant treatment

	Visit 1		Visit 2		Visit 3	
	N	%	N	%	N	%
Methotrexate + Analgesics + Systemic glucocorticoids	8	12.9%	3	4.8%	2	3.2%
Systemic glucocorticoids only	6	9.7%	9	14.5%	15	24.2%
Systemic glucocorticoids + analgesics	7	11.3%	3	4.8%	4	6.5%
Analgesics only	8	12.9%	6	9.7%	3	4.8%
No concomitant RA treatment (tofacitinib only)	3	4.8%	12	19.4%	9	14.5%

In total, antidepressants, anxiolytics and hypnotics were used by 6.5%, 1.6% and 8.1% of patients, respectively. The changes of these counts are demonstrated in the table below. The mean dosing of these medicines and its changes were not analyzed due to a low number of records in each category.

Table 31 Concomitant treatment of mental illnesses per study visit

	Visit 1		Visit 2		Visit 3	
	N	%	N	%	N	%
Antidepressants	4	6.5%	2	3.2%	5	8.1%
Citalopram	2	3.2%	1	1.6%	2	3.2%
Escitalopram	0	0.0%	1	1.6%	2	3.2%
Sertraline	1	1.6%	0	0.0%	1	1.6%
Trazodone	1	1.6%	0	0.0%	1	1.6%
Venlafaxine	1	1.6%	0	0.0%	0	0.0%
Anxiolytics	1	1.6%	0	0.0%	0	0.0%
Alprazolam	1	1.6%	0	0.0%	0	0.0%
Hypnotics	5	8.1%	3	4.8%	2	3.2%
Zolpidem	5	8.1%	3	4.8%	2	3.2%

*The table displays an overview of all medicines with an occurrence in at least one patient.

10.4.2.9. Absolute change of DAS28-4 score

The DAS28-4 score serves as an integral value of the disease status. Independently if a DAS28-4 score was calculated based ESR or CRP, the final scores are considered comparable because DAS28-4(CRP) has the same validation profile as DAS28-4(ESR)(9). To enable an interpretation of DAS28-4 results across the entire study population, there was

no differentiation made between DAS28-4 (ESR) and DAS28-4(CRP), both scores are presented as DAS28-4 in this section.

The DAS28 score is interpreted as followed:

<2.6 RA in remission

2.6-3.2 low level of disease activity

3.2-5.1 active disease, may require change of treatment

>5.1 very active disease, requires careful monitoring and change of treatment

Mean (SD) DAS28-4 score at Visit 1 was 5.86 (±0.85).

After 6 months of tofacitinib treatment the mean DAS28-4 score decreased by 3.01 (± 1.19). In total, after 12 months from the start of tofacitinib treatment the mean DAS28-4 score decreased by 3.06 (± 1.41). The final mean score of 2.79 (±1.09) indicating an overall lower disease activity.

Table 32 DAS28-4

	N	Mean	SD	Median	IQR	Min	Max
DAS28-4 at Visit 1	62	5.86	0.85	5.8	1.1	3.5	8.0
DAS28-4 at Visit 2	62	2.85	1.06	2.8	1.2	1.1	6.4
DAS28-4 at Visit 3	62	2.79	1.09	2.7	1.2	1.1	6.6
Absolute change of DAS28-4 from Visit 1 at Visit 2	62	-3.01	1.19	-3.2	1.6	-5.4	0.1
Absolute change of DAS28-4 from Visit 1 at Visit 3	62	-3.06	1.41	-3.1	1.8	-5.5	1.1

10.4.2.10. Remission as assessed by DAS28-4 < 2.6

DAS28-4 score lower than 2.6 indicates the RA being in remission. In total, after 12 months of tofacitinib treatment, 26 out of 62 patients (41.9%) reached the DAS28-4 score lower than 2.6.

Table 33 DAS28-4 < 2.6

	N	%
DAS28-4 < 2.6		
Visit 1	0	0.0%
Visit 2	27	43.5%
Visit 3	26	41.9%

10.4.2.11. LDA as assessed by DAS28-4 <3.2

DAS28-4 score lower than 3.2 indicates a low level of RA activity or the RA being in remission. In total, after 12 months of tofacitinib treatment, 44 out of 62 patients (71.0%) reached the DAS28-4 score lower than 3.2.

Table 34 DAS28-4 < 3.2

	N	%
DAS28-4 < 3.2		
Visit 1	0	0.0%
Visit 2	40	64.5%
Visit 3	44	71.0%

10.4.2.12. Change in EuroQol Three Dimension – 3L (EQ-5D-3L) Health State Profile

The EQ-5D-3L Index score summarizes each possible health state on a numerical scale ranging from -0.594 – 1. A score of 1 indicates full health, score of 0 indicates a state equivalent to being dead, and score lower than 0 indicates a state equivalent to the worst possible health status.

In total, after 12 months of tofacitinib treatment, the mean score (EQ-5D-3L Index score) increased from 0.541 to 0.720, i.e. the mean increase of utility was 0.179.

Table 35 EQ-5D-3L index score

	N	Mean	SD	Median	IQR	Min	Max
EQ-5D-3L score at Visit 1	62	0.541	0.241	0.604	0.173	-0.074	1.000
EQ-5D-3L score at Visit 2	62	0.698	0.152	0.691	0.140	0.150	1.000
EQ-5D-3L score at Visit 3	62	0.720	0.178	0.691	0.209	0.189	1.000
Absolute change of EQ-5D-3L utility between Visit 1 and Visit 2	62	0.157	0.231	0.104	0.197	-0.175	1.016
Absolute change of EQ-5D-3L utility between Visit 1 and Visit 3	62	0.179	0.271	0.104	0.270	-0.502	1.016

The EQ-5D-3L VAS score is rated on a scale of 0-100 points. While 0 points represent the worst possible health status, 100 points represent the best possible health status.

In total, after 12 months of tofacitinib treatment, the mean EQ-5D-3L VAS score increased from 49.66 (±19.5) points to 74.37 (±18.19) points, i.e. the mean increase of 24.71 (±27.65) points.

Table 36 EQ-5D-3L VAS score

	N	Mean	SD	Median	IQR	Min	Max
EQ-5D-3L VAS score at Visit 1	62	49.66	19.50	50.0	33.5	10.0	90.0
EQ-5D-3L VAS score at Visit 2	62	68.69	19.34	70.0	24.5	0.0	99.0
EQ-5D-3L VAS score at Visit 3	62	74.37	18.19	78.5	25.0	25.0	100.0
Absolute change of EQ-5D-3L VAS score between Visit 1 and Visit 2	62	19.03	27.81	20.0	40.8	-50.0	66.0
Absolute change of EQ-5D-3L VAS score between Visit 1 and Visit 3	62	24.71	27.65	24.0	41.0	-45.0	75.0

10.5. Other analyses

10.5.1. Hierarchical structural equation model

The objective of this analysis was to determine the extent to which changes in depression, as measured by CUDOS, are mediated by changes of disease activity, as measured by the change of DAS28-4 score. Additionally, the study considered the impact of arthritis on patients' lives, measured by the VAS, as a potential mediator in this relationship.

The standardized residual variances for CUDOS at Visit 2 and Visit 3 are 0.662 and 0.764, respectively. This indicates that 66.2% and 76.4% of the variance in depression scores at these visits are due to factors other than disease activity and arthritis impact (as remain unexplained by the model). Therefore, while tofacitinib appears to reduce depression partly through its impact on disease activity, a substantial portion of its effect on depression is likely mediated by other mechanisms.

In contrast, the path coefficient for the effect of change in DAS28 on CUDOS at Visit 3 (0.492) is statistically significant (p-value < 0.001), indicating a medium to large effect size. This suggests that reductions in disease activity are associated with a substantial decrease in depression symptoms at Visit 3. Specifically, a one standard deviation decreases in DAS28 results in an approximately 49.2% standard deviation decrease in CUDOS scores at Visit 3.

The model demonstrates a less-than-ideal fit, suggesting that more variables and predictors should be incorporated to adequately describe the mechanisms of underlying changes in CUDOS. This inadequacy is evident from the large proportion of unexplained variability in the model. In order to have more meaningful results based on this model a bigger patient number would be required.

For more details of this model see Section 15.

10.5.2. Linear mixed-effect model

The aim of this exploratory analysis was to describe the impact of depression, anxiety, sleep and the level of arthritis impact on patients' lives (measured by CUDOS, CUXOS, JSEQ and VAS score respectively) on the generic quality of life (measured by EQ-5D utility score).

In total, 147 measurements (V1; n= 38, V2; n=48 and V3; n=61) were used in the model as the question regarding the VAS score was added to the eCRF later, so not all patients have these data available at all visits. We use all available 147 measurements to utilize all possible information and achieve high precision, as LME models are specifically designed to handle unbalanced data and missing measurements effectively.

The linear mixed-effects model results indicate that depression (CUDOS) and level of arthritis impact (VAS) have a significant negative impact on the EQ-5D utility score, with each unit increase in CUDOS and VAS associated with decreases of 0.008 (p = 0.001) and 0.002 (p < 0.001) in EQ-5D score, respectively. Anxiety (CUXOS) and sleep (JSEQ) were not significant predictors. The model accounted for patient-level variability, with a random intercept variance of 0.01016, and demonstrated a good fit, as evidenced by well-behaved residuals. These findings suggest that higher depression and higher VAS scores are associated with lower quality of life, while anxiety and sleep did not show a significant impact on quality of life.

For more details of this model see Section 15.

10.6. Adverse events / adverse reactions

10.6.1. Brief summary of AE

In total, there were 22 safety events reported in this observational study. Out of 70 patients, there were 15 patients (21.4%) who experienced at least 1 AE. For the full list of adverse events from this study, see Section 15.

The total number of reported adverse events (AEs) was 22, of which:

- 1 was reported as serious AE related to tofacitinib
- 1 was reported as non-serious AE related to tofacitinib;
- 19 were reported as non-serious AE not-related to tofacitinib;
- 1 was reported as non-serious AE - causality unknown.

Table 37 AE overview per causality and seriousness

Causality	Seriousness	N*	%
Yes	Serious	1	4.5%
	Non-serious	1	4.5%
No	Serious	0	0%
	Non-serious	19	86.4%
Unknown	Serious	0	0%
	Non-serious	1	4.5%

*N=22

10.6.2. Types of adverse events reported within this study

There were 3 types of AE reported in this study:

- Serious adverse events
- Non-serious adverse events
- Scenarios involving exposure to a drug under study (e.g. lack of efficacy)

10.6.2.1. Serious adverse events

There was one serious adverse event (thrombocytopenia) reported within this study. The Investigator assessed this event to be related to tofacitinib. The incidence of thrombopenia (SOC: Blood and lymphatic system disorders) was 1.4% (1 patient out of 70).

Table 38 Serious adverse events

	N	%
Number (%) of Patients:		
Evaluable for adverse events	70	100.0%
With adverse events	1	1.4%
Number (%) of Patients with Adverse Events by System Organ Class and MedDRA	**N**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1.4%
Thrombopenia	1	1.4%

10.6.2.2. Non-serious adverse events

There were 21 non-serious adverse events reported within this study, out of them 5 AE belong to the type: Scenarios involving exposure to a drug under study (lack of efficacy).

Table 39 Non-serious adverse events

	N	%
Number (%) of Patients:		
Evaluable for adverse events	70	100.0%
With adverse events	15	21.4%
Number (%) of Patients with Adverse Events by System Organ Class and MedDRA	**N**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1.4%
Thrombopenia	1	1.4%
EAR AND LABYRINTH DISORDERS	1	1.4%
Vertigo	1	1.4%
EYE DISORDERS	1	1.4%
Dryness of eyes	1	1.4%

Table 39 Non-serious adverse events

	N	%
GASTROINTESTINAL DISORDERS	1	1.4%
Dryness oral	1	1.4%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5	7.1%
Drug effect lack of	5	7.1%
INFECTIONS AND INFESTATIONS	10	14.3%
Acute bronchitis	1	1.4%
Cold	1	1.4%
COVID-19	3	4.3%
Nasopharyngitis	1	1.4%
Post herpetic neuralgia	1	1.4%
Shingles	1	1.4%
Virosis	2	2.9%
RENAL AND URINARY DISORDERS	1	1.4%
Haematuria	1	1.4%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	1.4%
Cough	1	1.4%

11. DISCUSSION

11.1. Key results

The primary objective of this study was to describe and evaluate the changes of depression level after 12 months from the start of tofacitinib therapy in patients with RA and at least minimal level of depression. The primary research question was to find out if treatment with tofacitinib reduces the depression level by at least 10% after 12 months, based on the Clinically Useful Depression Outcome Scale score.

The final score of CUDOS questionnaire ranges from 0 to 72, the higher the score, the more severe the depression. The mean CUDOS score at the start of tofacitinib treatment was 21.97 points, which decreased to the mean score of 9.29 points after 12 months of tofacitinib treatment. The mean change of CUDOS score after 12 months of tofacitinib treatment (a decrease of 12.68 points) is considered statistically significant, with a p-value < 0.001.

The primary outcome of this study indicates that the depression level of patients with rheumatoid arthritis decreases after 12 months of tofacitinib treatment by more than 10%. The mean decrease of CUDOS score in 62 patients observed in this non-interventional study was 53.1%..

Furthermore, the decrease in depression could already be seen 6 months after tofacitinib start with a decrease by 9.18 points of the CUDOS score and a significant difference in CUDOS scores between Visit 1 and Visit 2 (p-value < 0.001).The secondary objectives of this study were to describe and evaluate the level and changes of RA impact on patients´ life, anxiety, and insomnia in patients with RA and at least minimal level of depression.

The anxiety level in RA patients with at least a minimal level of depression was evaluated using the Clinically Useful Anxiety Outcome Scale score. The final score of CUXOS questionnaire ranges from 0 to 80, the higher the score, the more severe the anxiety. The mean CUXOS score at the start of tofacitinib treatment was 20.45 points, which decreased to the mean score of 8.21 points after 12 months of tofacitinib treatment. The mean change of CUXOS score within 12 months of tofacitinib treatment was a decrease of 12.24 points, i.e. a decrease by 47.1%. An additional analysis of CUXOS scores reported after 6 months of tofacitinib treatment demonstrates that the effect on anxiety level had already been present. The mean change of CUXOS score after 6 months of tofacitinib treatment is a decrease by 8.21 points, i.e. by 33.2%.

The insomnia level in RA patients with at least a minimal level of depression was evaluated using the Jenkins Sleep Evaluation Questionnaire (7). The final score of JSEQ questionnaire ranges from 0 to 20, the higher the score, the lower the sleep quality. The mean JSEQ score at the start of tofacitinib treatment was 9.40 points, which decreased to the mean score of 5.48 points after 12 months of tofacitinib treatment. The mean change of JSEQ score within 12 months of tofacitinib treatment was a decrease of 3.92 points, i.e. a decrease by 34.5%. An additional analysis of JSEQ scores reported after 6 months of tofacitinib treatment demonstrates that the effect on insomnia level had already been present. The mean change of JSEQ score after 6 months of tofacitinib treatment is a decrease of 2.77 points, i.e. by 27.6%.

The level of impact of arthritis on patient’s life in RA patients with at least a minimal level of depression was evaluated using the Visual Analogue Scale. The final score of VAS ranges from 0 to 100, the higher the score, the higher impact of arthritis on patient’s life (10). The mean VAS score at the start of tofacitinib treatment was 61.42 points, which decreased to the mean score of 33.75 points after 12 months of tofacitinib treatment. The mean change of VAS score within 12 months of tofacitinib treatment was a decrease of 27.55 points, i.e. a decrease by 35.4%. An additional analysis of VAS scores reported after 6 months of tofacitinib treatment demonstrates that the effect on VAS score had already been present. The mean change of VAS score after 6 months of tofacitinib treatment is a decrease of 29.58 points, i.e. by 43.4%.

At the start of the tofacitinib treatment the mean DAS28-4 score (11) was 5.86, which indicates a very active disease. After 12 months of tofacitinib treatment the mean DAS28-4 score decreased to 2.79, which indicates a low level of disease activity. DAS28-4 score lower than 3.2, which indicates a low level of RA activity or the RA being in remission, was after 12 months of tofacitinib treatment recorded in 44 out of 62 patients (71.0%).

The EQ-5D-3L Index score describing patients´ health state increased from the mean utility 0.541 to 0.720, i.e. the mean increase of utility was 0.179.

The safety evaluations confirm the risk-profile of tofacitinib treatment as a medication with a low frequency of adverse events.

11.2. Limitations

The study did not reach the sample size required to allow full interpretation of all of the results found in the study. While the sample size was sufficient for the paired t-test analysis showing significant decrease in depression and anxiety, it was too low for interpretation of all the underlying factors. The hierarchical structural equation model demonstrates a less-than-ideal fit, suggesting that more variables and predictors should be incorporated to adequately describe the mechanisms underlying changes in CUDOS. In order to get reliable and valid results from this model, a higher number of patients would be needed. Hence, this study could show a significant decrease in depression, but interpretation of the results is not possible due to a lack of proof for the underlying cause of changes in depression and anxiety seen in this population.

This study clearly shows a significant reduction in depression and anxiety as measured with the CUDOS and CUXOS scales in patients with tofacitinib as treatment for rheumatic arthritis. The decrease can be seen after 6 months and is maintained after 12 months. To be able to make a valid conclusion on why patients showed reduced signs of depression and anxiety a higher sample size would be required.

11.3. Generalizability

The data cannot be generalized, because the relationship between treatment with tofacitinib and changes in depression could not be clarified with the number of patients the study was able to recruit.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

In Patient with rheumatoid arthritis, after 12 months of tofacitinib treatment in this study reduction in depression of more than 10% was observed. In addition, to that the level of anxiety, insomnia and impact of the disease on patient´s life decreased as well. These are descriptive results that do not support any further conclusions. Additional exploration is needed to control for confounders and permit analysis of causality.

14. REFERENCES

1. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.

2. Baliga S, Samant R, Balakrishnan CAB0337 MENTAL HEALTH AND RHEUMATOID ARTHRITISAnnals of the Rheumatic Diseases 2023;82:1351-1352.

3. Young LD. Psychological factors in rheumatoid arthritis. J Consult Clin Psychol. 1992;60(4):619–27.

4. Kotsis K, Voulgari PV, Tsifetaki N, Machado MO, Carvalho AF, Creed F, et al. Anxiety and depressive symptoms and illness perceptions in psoriatic arthritis and associations with physical health-related quality of life. Arthritis Care Res. 2012 Oct;64(10):1593–601.

5. Zimmerman M, Chelminski I, McGlinchey JB, Posternak MA. A clinically useful depression outcome scale. Compr Psychiatry. 2008 Apr;49(2):131–40.

6. Zimmerman M, Chelminski I, Young D, Dalrymple K. A clinically useful anxiety outcome scale. J Clin Psychiatry. 2010 May;71(5):534–42.

7. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol. 1988;41(4):313–21.

8. Saliba A, Ostojic P. Personality and participation: Who volunteers to participate in studies. Psychology. 2014;5(3):230-243.

9. Hayes MHS, Patterson DG. (1921) Experimental development of the graphic rating method. Psychological Bulletin, 18, 98-99.

10. Wells G, Becker JC, Teng J, Dougados M, Schiff M, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann of the Rheum Dis. 2009;(68)6:954-960.

11. Aletada D, Ward MM, Machold KP, Nell VPK, et al. Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. Arthritis & Rheumatism. 2005;52(9), 2625-2636.

15. LIST OF SOURCE TABLES AND FIGURES

.Table 1 Demographic characteristics (Safety population)

	Male	Female	Total
Number (%) of Patients:	9	61	70
Age (years):			
< 18	0 (0.0%)	0 (0.0%)	0 (0.0%)
18-44	3 (33.3%)	11 (18.0%)	14 (20.0%)
45-64	4 (44.4%)	28 (45.9%)	32 (45.7%)
>= 65	2 (22.2%)	22 (36.1%)	24 (34.3%)
Mean	51.2	58.2	57.3
SD	17.1	12.7	13.4
Range	25-75	23-77	23-77
Weight (kg):			
Mean	88.4	75.1	76.8
SD	19.1	15.0	16.1
Range	65-118	50-118	50-118
N	9 (100.0%)	61 (100.0%)	70 (100.0%)
Height (cm):			
Mean	182.7	167.6	169.5
SD	10.0	5.4	7.9
Range	160-198	150-179	150-198
N	9 (100.0%)	61 (100.0%)	70 (100.0%)
BMI:			
Mean	26.5	26.7	26.7
SD	5.2	5.3	5.3
Range	18.8-34.5	18.4-41.3	18.4-41.3
N	9 (100.0%)	61 (100.0%)	70 (100.0%)

Table 2 Overview of all observed comorbidities

N=62	**N**	**%**
Co-morbidities	43	69.4%
Cardiovascular diseases	24	38.7%
Myocardial infarction	1	1.6%
Angina pectoris	0	0.0%
Heart failure	0	0.0%
Arrhythmia	3	4.8%
Hypertension	19	30.6%
Stroke	2	3.2%
Peripheral vascular disease	3	4.8%
Other	1	1.6%
Malignancies	0	0.0%
Metabolic/endocrine disorders	25	40.3%
Hypothyroidism	6	9.7%
Hyperthyroidism	0	0.0%
Type I diabetes mellitus	1	1.6%
Type II diabetes mellitus	5	8.1%
Dyslipidemia	15	24.2%
Other	2	3.2%
Gastrointestinal diseases	9	14.5%
Gastroduodenal ulcer	3	4.8%
Diverticulosis	3	4.8%
Crohn's disease	0	0.0%
Ulcerative colitis	0	0.0%
Other	3	4.8%
Musculoskeletal disorders	19	30.6%
Osteoporosis	9	14.5%
Osteopenia	2	3.2%
Osteoarthrosis	9	14.5%
Entrapment syndrome	0	0.0%
Vertebrogenic algic syndrome	1	1.6%
Other	1	1.6%
Pulmonary diseases	2	3.2%
COPD	1	1.6%
Bronchial asthma	0	0.0%
Chronic bronchitis	1	1.6%
Other	0	0.0%
Psychiatric disorders	6	9.7%
Periodic depressive disorder	5	8.1%
Dysthymia	0	0.0%
Bipolar affective disorder	0	0.0%
Generalized anxiety disorder	0	0.0%

Table 2 Overview of all observed comorbidities

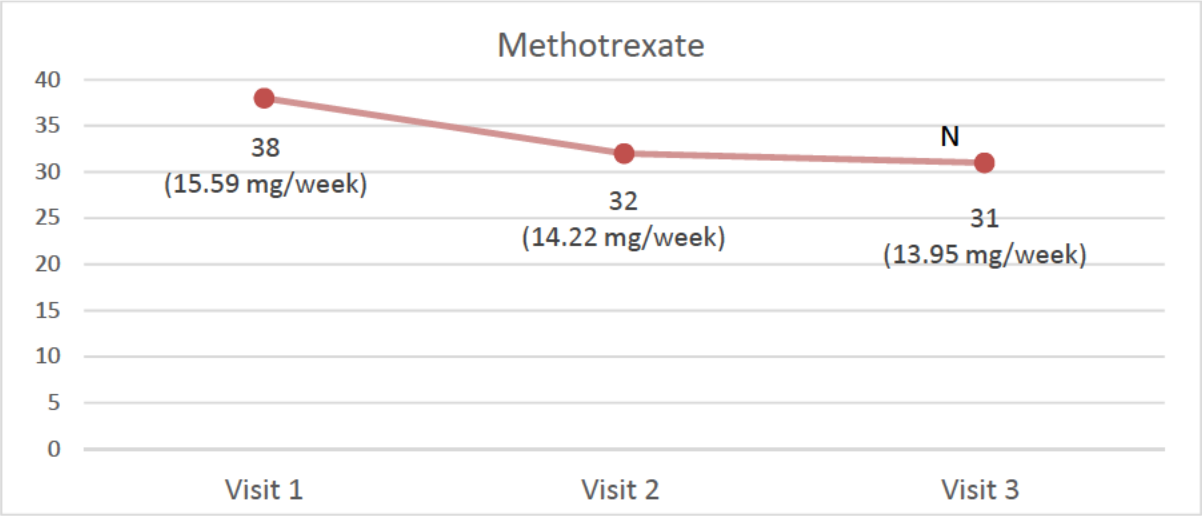
N=62	N	%
Panic disorder	0	0.0%
Agoraphobia	0	0.0%
Specific phobia	0	0.0%
Social phobia	1	1.6%
Obsessive compulsive disorder	0	0.0%
Non-organic sleep disorder	0	0.0%
Psychotic illness	0	0.0%
Sexual disorders	0	0.0%
Other	0	0.0%
Urological/renal diseases	5	8.1%
Chronic kidney disease	1	1.6%
Glomerulonephritis	0	0.0%
Urolithiasis	3	4.8%
Other	1	1.6%
Other diseases	5	8.1%

.Table 3 Tofacitinib dosing – discontinued patients

	Total	Tofacitinib dose					
		11 mg/once a day		5 mg once a day		5 mg/twice a day	
		N	%	N	%	N	%
Visit 1	8	2	25.0%	0	0.0%	9	75.0%
Visit 2	4	2	50.0%	0	0.0%	2	50.0%
Visit 3	0	0	0.0%	0	0.0%	0	0.0%

.Table 4 Methotrexate mean dose per study visit

	N (%)	Average dose (mg/week)	SD (mg/week)	Median (mg/week)
Visit 1	38 (61.3 %)	15.59	5.18	15
Visit 2	32 (51.6 %)	14.22	5.4	15
Visit 3	31 (50.0 %)	13.95	5.39	15



.Figure 1 Patients with methotrexate and their mean weekly dose

[redacted]

.Table 5 Hierarchical structural equation model

Hierarchical structural equation model

Path coefficients

Path	Estimate	Standardized	P-value
CUDOS at Visit 2			
CUDOS(V2) ~ CUDOS(baseline)	0.38	0.392	0.001
CUDOS(V2) ~ changeDAS28(V2	0.88	0.124	0.302
CUDOS(V2) ~ VAS(V2)	0.14	0.335	0.004
VAS at Visit 2			
VAS(V2) ~ changeDAS28(V2)	5.45	0.328	0.016
CUDOS at Visit 3			
CUDOS(V3) ~ CUDOS(baseline)	0.10	0.15	0.239
CUDOS(V3) ~ changeDAS28(V3	2.01	0.492	<0.001
CUDOS(V3) ~ VAS(V3)	-0.05	-0.217	0.075
VAS at Visit 3			
VAS(V3) ~ changeDAS28(V3)	4.83	0.261	0.061

Variances

Variable	Estimate	Standardized variance	% Unexplained variability
CUDOS(V2)	49.19	0.662	66.20%
VAS(V2)	361.51	0.892	89.20%
CUDOS(V3)	26.53	0.764	76.40%
VAS(V3)	660.22	0.932	93.20%

Estimate - The unstandardized coefficient represents the raw relationship between two variables in their original units. It tells us how much the dependent variable changes for a one-unit change in the independent variable. For example, if the estimate is 0.88 for CUDOS(V2) ~ changeDAS28(V2), it means that for each one-unit increase in changeDAS28(V2), CUDOS(V2) increases by 0.88 units.

Standardized coefficient - The standardized coefficient represents the relationship between two variables in standardized units (z-scores), where each variable has a mean of 0 and a standard deviation of 1. It tells us how many standard deviations the dependent variable will change for a one standard deviation change in the independent variable. For example, a standardized coefficient of 0.124 for CUDOS(V2) ~ changeDAS28(V2) means that for each one standard deviation increase in changeDAS28(V2), CUDOS(V2) increases by 0.124 standard deviations.

.Table 6 Linear mixed-effect model

Linear mixed-effect model: EQ5D ~ CUDOS + CUXOS + JSEQ + VAS + (1 | patient ID)

	Estimate	Standard error	P-value	Significance
Intercept	0.887	0.033	-	
CUDOS	-0.008	0.002	0.001	**
CUXOS	-0.002	0.002	0.395	
JSEQ	-0.003	0.005	0.504	
VAS	-0.002	0.001	< 0.001	***

.Table 7 Overview of adverse events

No.	Patient ID	Seriousness	Visit	medDRA LLT	Causality	medDRA code	medDRA SOC
1	601	serious	V3	Thrombopenia	Yes	10043569	Blood and lymphatic system disorders
2	200002	non-serious special situation	V3	Drug effect lack of	No	10013684	General disorders and administration site conditions
3	631	non-serious special situation	V2	Drug effect lack of	No	10013684	General disorders and administration site conditions
4	200003	non-serious special situation	V3	Drug effect lack of	Unknown	10013684	General disorders and administration site conditions
5	674	non-serious special situation	V3	Drug effect lack of	No	10013684	General disorders and administration site conditions
6	672	non-serious special situation	V2	Drug effect lack of	Yes	10013684	General disorders and administration site conditions
7	2	non-serious	V2	Cold	No	10009851	Infections and infestations
8	651	non-serious	V2	Virosis	No	10065957	Infections and infestations
9	618	non-serious	V2	Vertigo	No	10047340	Ear and labyrinth disorders
10	605	non-serious	V2	COVID-19	No	10084268	Infections and infestations
11	510	non-serious	V2	Shingles	No	10040555	Infections and infestations
12	651	non-serious	V3	Virosis	No	10065957	Infections and infestations
13	651	non-serious	V3	Cough	No	10011224	Respiratory, thoracic and mediastinal disorders
14	616	non-serious	V3	COVID-19	No	10084268	Infections and infestations
15	616	non-serious	V3	Dryness of eyes	No	10013792	Eye disorders
16	616	non-serious	V3	Dryness oral	No	10028021	Gastrointestinal disorders
17	607	non-serious	V3	Thrombocytopenia	No	10043569	Blood and lymphatic system disorders
18	507	non-serious	V3	Haematuria	No	10018867	Renal and urinary disorders
19	507	non-serious	V3	COVID-19	No	10084268	Infections and infestations
20	510	non-serious	V3	Post herpetic neuralgia	No	10036376	Infections and infestations
21	515	non-serious	V3	Acute bronchitis	No	10000687	Infections and infestations
22	522	non-serious	V3	Nasopharyngitis	No	10028810	Infections and infestations