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Report on results

Rapid Data Analysis – Tofacitinib and psychiatric disorders

Background	
Short title of topic	Association of tofacitinib with psychiatric disorders
Contact	ICU@ema.europa.eu
Regulatory procedure	Signal on psychiatric disorders with tofacitinib
Background	A signal of psychiatric disorders with tofacitinib has been identified and was discussed by PRAC at its September 2020 PRAC meeting. The signal will be further assessed as part of the next PSUR for the substances (submission by 14 January 2021). Feasibility to support assessment of this signal has been explored by EMA by reviewing exposure and event rates for JAK inhibitors and other substances indicated for treatment of rheumatoid arthritis. Results are provided as part of Annex 4.

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Background	
Description of research question	Psychiatric events recorded in association with treatment of adult patients with rheumatoid arthritis with tofacitinib, baricitinib or tocilizumab. • to describe incidence rates of psychiatric events occurring in association with tofacitinib, baricitinib or tocalizumab o in patients with history of psychiatric events o in patients without history of psychiatric events • to describe characteristics of patients experiencing psychiatric events occurring in association with tofacitinib, baricitinib or tocilizumab.

Table of Contents

PART I: Analysis Protocol

1. List of abbreviations

EMA	*European Medicines Agency*
MAH	*Marketing Authorisation Holder*
MS	*Member State*
PRAC	*Pharmacovigilance Risk Assessment Committee*
PSUR	*Periodic Safety Update Report*
RDA	*Rapid Data Analysis*

2. Amendments and updates

Additional data analyses were carried out post-hoc not limiting the analyses to patients with prior diagnoses of rheumatoid arthritis only as well as providing survival curves for the outcomes under the different treatments (see section 10.4 and Annex 2 for results).

3. Milestones

Milestone	Planned date
Feasibility feedback with analysis proposal shared with Rapporteur	24 September 2020
Draft analysis protocol circulated to Rapporteur and PRAC Members for comments	3 November 2020
Comments from Rapporteur and PRAC Members on draft analysis plan by	13 November 2020
Updated analysis plan following comments circulated by EMA to Rapporteurs and PRAC Members by	20 November 2020
Internal analysis report by EMA circulated to Rapporteurs and PRAC Members by	10 December 2020
Registration of public report in the EU PAS register (including study report)	*Once protocol and analysis are finalised, TBA*

4. Rationale and background

A signal of psychiatric disorders with tofacitinib has been identified based on case reports describing psychiatric events such as suicidal ideation and anxiety.

The MAH for tofacitinib has therefore been requested to provide further review of information psychiatric disorders for the next PSUR.

Tofacitinib belongs to the class of JAK-inhibitors. Other members of the class are baricitinib as well as roxulitinib and updadicitinib.

Tofacitinib is approved under the trade name Xeljanz and is indicated in the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. Baricitinib is approved under the trade name Olumiant and is indicated in the treatment of rheumatoid arthritis.

The prevalence of mood disturbances such as anxiety and depression is greater in rheumatoid arthritis (RA) patients than in the general population [Peterson et al. 2019, Margaretten et al 2011].

A 2013 meta-analysis reported a 17% pooled prevalence of major depressive disorder and a 39% prevalence of depression using the Patient Health Questionnaire-9 (PHQ-9) in patients with RA [Matcham et al. 2013].

The prevalence of anxiety in RA is approximately half that of depression and estimated to lie between 13—20%. When this is compared to the prevalence of depression and anxiety in the general population (with the 2014 Adult Psychiatric Morbidity Survey reporting that 5.9% and 3.3% of the adult English population suffered from generalised anxiety disorder and a depressive disorder, respectively), it is clear that patients with RA have a significantly increased mental health burden [Scott et al 2018].

A proposed disease model suggests that RA disease activity and physical and mental health are connected via central neuroendocrine pathways as well as altered dopaminergic pathways, resulting in abnormal pain processing, negative affect, and maladaptive coping strategies, contributing ultimately to physical and psychosocial distress in some patients [up-to-date, Overview of the systemic and non-articular manifestations of rheumatoid arthritis].

Both Olumiant and Xeljanz are alongside other approved indications indicated for moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to one or more disease-modifying antirheumatic drugs. Considering the relatively high RA disease activity in the patient population treated with Olumiant and Xeljanz and the strong association of RA with anxiety and depression, there is a risk of confounding by indication in the setting of use for RA.

Tocilizumab is a monoclonal antibody acting as Interleukin-6 inhibitor and is indicated – amongst other indication – for second-line treatment of adult patients with RA. Based on its use as second line treatment for RA, it has been selected as additional substance for descriptive analyses to inform on event rates observed after treatment, although noting that only descriptive analyses and no comparative analyses are foreseen as part of the data analyses.

To support the further evaluation of the signal, a descriptive analysis will be performed using the IMS® Disease Analyzer Database. Patients receiving tofacitinib, baricitinib or tocilizumab will be included and followed up for occurrence of psychiatric events. Patient demographics (including indication for treatment if available) and incidence rates for patients with and without history of psychiatric events in patients receiving tofacitinib or baricitinib will be described.

The analysis will be restricted to adult patients receiving tofacitinib, baricitinib or tocilizumab for the indication of rheumatoid arthritis. First feasibility counts have shown that the majority of patients receive tofacitinib and baricitinib for these indications, while use in other indications is less prominent (963 patients receiving tofacitinib, 828 baricitinib and 357 tocilizumab in internal medicine practices from January 2017 until latest data availability).

A comparative analysis is not proposed at this stage due to anticipated low event counts and uncertain effect estimates. As baricitinib belongs to the same class of substances as tofacitinib with similar indications, it is proposed to provide results for this substance alongside tofacitinib. However, for the other JAK inhibitors currently approved the exposure in the available databases is not deemed

sufficient for analyses (see feasibility analysis in the annex). Tocilizumab has been chosen as additional substance based on its indication for second-line treatment of RA in adult patients.

The analysis will be restricted to patients receiving prescriptions by internal medicines specialists due to the structure of the IMS® Disease Analyzer database and German healthcare system to allow for continuous patient enrolment.

5. Research question and objectives

Psychiatric events recorded in association with treatment of tofacitinib, baricitinib or tocilizumab.

- to describe incidence rates of recorded psychiatric disorders occurring in association with tofacitinib, baricitinib or tocilizumab in adult patients with a diagnosis of rheumatoid arthritis (ICD 10 codes M05 and M06)
    - in patients with history of psychiatric events
    - in patients without history of psychiatric events
- to describe characteristics of adult patients with rheumatoid arthritis experiencing psychiatric events occurring in association with tofacitinib, baricitinib or tocilizumab.

6. Research methods

6.1. Study design

This will be a descriptive cohort study of patients initiating treatment with baricitinib, tofacitinib or tocilizumab from January 2017 to June 2020. Adult patients in internal medicine specialist practices with a minimum of 365 days of observation prior to the first initiation of baricitinib, tofacitinib or tocilizumab will be included in the analysis. Patient will be followed for psychiatric outcome events until the end of follow-up for the patient, which is the last consultation date for the patient.

6.2. Setting

The setting will be internal medicine specialist practices (‘internal medicine with focus’) prescribing baricitinib or tofacitinib in the IMS® Disease Analyzer Germany database.

Population:

The study population will include adult patients aged ≥18 years registered in the IMS® Disease Analyzer Germany database with a history of rheumatoid arthritis who are initiating treatment with baricitinib, tofacitinib or tocilizumab on or after 1 January 2017 and have at least 365 days of observation prior to the first prescription.

Study period:

The study period will be limited to the period from January 2017 (year of EU marketing authorisation for tofacitinib) to the latest database availability (June 2020) to assure recruiting patient from similar time periods and to reduce time-related treatment effects.

6.3. Variables

Exposure of interest: All prescriptions for tofacitinib, baricitinib or tocilizumab in the population of interest will be considered. Please see Annex 1 for the list of products.

Outcomes

Recording of the following outcome events will be analysed:

- Mania/bipolar or severe depression: ICD 10 codes F30 (manic episode), F31 (bipolar affective disorder), F32.3 (severe depressive episode with psychotic symptoms) and F33.3 (recurrent depressive disorder, current episode severe with psychotic symptoms)
- Other depression: ICD 10 codes F32.0-F32.2, F32.8-F32.9 (depressive episode), F33.0-F33.2, F33.8-F33.9 (recurrent depressive disorder)
- Other mood disorder: ICD 10 codes F34 (persistent mood disorders), F38 (other mood disorders), F39 (unspecified mood disorder), F41 (Other anxiety disorders), F42 (Obsessive-compulsive disorder), F43 (Reaction to severe stress, and adjustment disorders), F60.3 (emotionally unstable personality disorder), R45.0-R45.7 (symptoms and signs involving emotional state)
    - Other anxiety disorders (ICD 10 code F41)
    - Other mood disorders excluding other anxiety disorders (ICD 10 code F41)
- Schizophrenia-related disorder: ICD 10 codes F20 to F29 (schizophrenia, schizotypal and delusional disorders), R44.0 (Auditory hallucinations), R44.1 (Visual hallucinations), R44.2 (Other hallucinations), R44.3 (Hallucinations, unspecified), R44.8 (Other and unspecified symptoms and signs involving general sensations and perceptions)
- Suicidal and self-harm events: ICD 10 codes Z91.5 (personal history of self-harm), R45.8 (Other symptoms and signs involving emotional state such as suicidal ideation (tendencies)), and ICD codes Z91.8 (personal history of other specified risk-factors, not elsewhere classified), T14.9 (injury unspecified), Z72.8 (unspecified problem related to lifestyle) where associated with a medical event text indicating a suicidal or self-harm event
- Initiation of treatment with minor tranquilizers (products for treatment of insomnia not included): EphMRA ATC code N05C. Substances include alprazolam bromazepam, buspirone, chlordiazepoxide, clobazam, clorazepic acid, clotiazepam, diazepam, hydroxyzine, kawain (combinations), ketazolam, lorazepam, magnesium, medazepam, meprobamate (combinations), metaclazepam, nordazepam, orphenadrine in combination with reserpine, oxazepam, oxazolam, piper methysticum (kava), and prazepam.
- Initiation of treatment with antidepressants or mood stabilizers including combinations with psycholeptics: EphMRA ATC codes N06A and N06C. Substances include acorus calamus, agomelatine, agrimonia eupatoria, amitriptyline (combinations), amitriptylinoxide, hypericum (combinations), bupropion, citalopram, oxitriptan (combinations), clomipramine, desipramine, dibenzepine, dosulepin, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, griffonia simplicifolia (combinations), imipramine, lamotrigine, lithium, lofepramine, maprotiline, melitracen, mianserin, milnacipran, mirtazapine, moclobemide, nefazodone, nortriptyline, opipramol, paroxetine, phenylalanine, reboxetine, rhodiola rosea (combinations), sertraline, tianeptine, tranylcypromine (combinations), trazodone, trimipramine, tryptophan, tyrosine, venlafaxine, viloxazine, and vortioxetine.

- Initiation of antipsychotic treatment: EphMRA ATC code N05A. Substances include amisulpride, amipiprazole, asenapine, benperidol, bromperidol, cariprazine, chlorpromazine, chlorprothixene, chlopenthixol, clozapine, dixyrazine, fluanixone, flupentixol, fluphenazine (combinations), fluspirilene, haloperidol, levomepromazine, lurasidone, melperone, metofenazate, olanzapine, paliperidone, perazine, periciazine, perphenazine, pimozide, pipamperone, promazine, promethazine, prothipendyl, quetiapine, remoxipride, risperidone, sertindole, sulpiride, thioridazine, tiapride, trifluoperazine, trifluperidol, trifluprомazine, ziprasidone, zotepine, and zuclopenthixol.
- Initiation of treatment is defined as the first prescription for the specific substance within the ATC code in a patient with no prior prescription for the same substance-ATC code combination during the 365 days prior to start of the JAK inhibitor/tocilizumab.

Prior psychiatric history:

- History of any of the recorded diagnosis outcome events (ever recorded from time of availability of information)
- Any treatment with any of the treatment categories recorded as outcome events within 365 prior to first prescription of tofacitinib, baricitinib or tocilizumab:
    - Treatment with minor tranquilizers (EphMRA ATC code N05C)
    - Treatment with antidepressants or mood stabilizers (EphMRA ATC codes N06A, N06C)
    - Treatment with antipsychotics (EphMRA ATC code N05A)

Variables considered as part of analyses relating to patient characteristics:

- Age
- Gender
- History of use of other RA treatments categorised as NSAIDs (EphMRA ATC code M01A), systemic corticosteroids (EphMRA ATC codes H02A, H02B, M01B), sulfasalazine, methotrexate, leflunomide, azathioprine, TNF alfa blockers (EphMRA ATC code L04B), and hydroxychloroquine. Products containing sulfasalazine, methotrexate, leflunomide, azathioprine and hydroxychloroquine will be identified on the basis of the substance name.

6.4. Data sources

The data source will be IMS® Disease Analyzer Germany version June 2020. IMS® Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of GP practices are included in IMS® Disease Analyzer Germany. Data from IMS® Disease Analyzer Germany have been shown to be representative of German healthcare statistics (Becher et al. 2009, Rathmann et al. 2018).

Diagnoses are coded using WHO ICD 10 codes, and prescriptions are coded using EphMRA ATC codes and substance names.

6.5. Study size

Based on feasibility checks, the total number of patients treated in internal medicine specialist practices in IMS® Disease Analyzer Germany is 1247 for tofacitinib and 1046 for baricitinib. Of these patients, 1040 patients initiating tofacitinib and 882 patients initiating baricitinib had at least 365 days of observation prior to the first initiation. For the event rate of psychiatric events in all patients with at least 365 days of observation, not restricted to internal medicine specialist practices, please see Annex 4 Feasibility Feedback.

6.6. Data management

Analyses will be conducted using SAS Enterprise Guide v 7.15.

The analyses will follow the objectives and will be run in the databases indicated.

6.7. Data analysis

Patients with any of the outcome events ever up to the first prescription for tofacitinib, baricitinib or tocilizumab will be considered to have a psychiatric history Patients will also be considered to have a psychiatric history if they have received treatment with minor tranquilizers, antidepressants/mood stabilizers or antipsychotics within the last 365 days prior to initiation of treatment with tofacitinib, baricitinib or tocilizumab.

For the definition and categorization of outcome events, please see section 6.3. “Other mood disorders” will also be sub-grouped into “Other anxiety disorders (ICD 10 code F41)” and “Other mood disorders” excluding ICD 10 code F41. For treatment as an outcome event initiation of new treatment will be considered whereas continuation of the same treatment will not be considered, please see section 6.3.

Patients will be followed for a maximum of 365 days after each prescription and will be considered to have a continuous treatment episode if the distance between prescriptions is 365 days or less. Observation for outcome events will be restricted to the first treatment episode for the patient. However, in case of a prescription for baricitinib or tocilizumab during the first treatment episode for tofacitinib or a prescription for tofacitinib or tocalizumab during the first treatment episode for baricitinib or a prescription for baricitinib or tofacitinib during the first treatment episode for tocilizumab the observation period will end on the date of the first prescription for the other treatment.

The incidence rate of the different outcome events will be calculated per patient-year of exposure.

A descriptive analysis will also be performed where baseline characteristics will be compared in patients with and patients without neuropsychiatric outcome events. These baseline characteristics will include mean and median age, gender, mean number of days between the first and last prescriptions for tofacitinib, baricitinib or tocilizumab, and history of use of other RA treatment (percent of patients) categorised as NSAIDs, systemic corticosteroids, sulfasalazine, methotrexate, leflunomide, azathioprine, TNF alfa blockers and hydroxychloroquine. Use of other RA treatment during tofacitinib, baricitinib or tocilizumab treatment episodes will also be summarised and compared in patients with and patients without neuropsychiatric outcome events.

6.8. Quality control

The code used for execution of the study will be saved.

6.9. Limitations of the research methods

It is anticipated that recording of psychiatric events in the databases might be incomplete as the patient may consult another physician or specialist or may be hospitalised for the event, which may or may not be recorded by the treating physician.

The occurrence of psychiatric events is known to be higher in patients with rheumatoid arthritis compared to the general population. This study will provide incidence rates of psychiatric events in patients treated with tofacitinib, baricitinib or tocilizumab, with and without a psychiatric history. No analysis of the causal relationship between the treatment and the occurrence of psychiatric events will be made. Possible confounding by indication will not be addressed as part of the foreseen descriptive analyses.

Initial feasibility analyses indicate low event rates and therefore any results might be based on small event number with associated uncertainties.

In Germany the patient has free physician choice: in IMS® Disease Analyzer Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete. The analysis is therefore restricted to patients overseen by internal medicines specialists.

6.10. Other aspects

n.a.

7. Protection of human subjects

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data are presented.

For IMS® Disease Analyzer France, cell counts of less than 20 will be suppressed in any output to be released into the public domain in order to prevent identification of individuals.

8. Management and reporting of adverse events/adverse reactions

This study is based on electronic medical records making secondary use of data. No special adverse event reporting requirements apply.

9. Plans for disseminating and communicating study results

This study will be registered in the EU PAS Register. After finalisation of analyses, the protocol as well as an abstract of the study results will be published in the EU PAS Register.

PART II: Analysis Results

10. Results

10.1. Participants

Patients 18 years or older at the initiation of treatment (tofacitinib, baricitinib or tocilizumab) with at least 365 days of observation prior to initiation of treatment in internal medicine specialist practices ('internal medicine with focus') were included and were followed for up to 365 days after each prescription. Follow-up ended at the earliest occasion of a gap of 366 days or more between prescriptions (follow-up then ended on day 365 after the prescription that preceded the gap), in case of a switch to one of the other treatment groups (follow-up ended on the date of the switch) or in case of end of follow-up (i.e. last visit of the patient). Treatment for rheumatoid arthritis was considered concomitant if it occurred between the first and last prescription of the study treatment.

Analyses were performed in patients that had a prior diagnosis of rheumatoid arthritis (WHO ICD 10 codes M05 and M06). Adult patients with a history of juvenile arthritis (WHO ICD 10 codes M08 and M08) but no specific diagnosis of rheumatoid arthritis were also included in this group.

A total of 1891 patients 18 years or older initiated treatment with tofacitinib, baricitinib or tocilizumab and had at least 365 days of observation prior to the first prescription, please see Table 1. A total of 1380 patients (73.0%) had a prior diagnosis of rheumatoid arthritis (n=1375) or a prior history of juvenile arthritis and no prior history of rheumatoid arthritis (n=5) and were collectively considered as rheumatoid arthritis in this study.

Comparatively fewer patients in the tocilizumab group vs. patients treated with baricitinib or tofacitinib had a prior diagnosis of rheumatoid arthritis, 18.4% (66/359) vs. 95.0% (672/707) for baricitinib and 77.8% (642/825) for tofacitinib.

Table 1 Total number of patients and number of patients with rheumatoid arthritis

No. of patients	Tofacitinib	Baricitinib	Tocilizumab
All (%)	825 (43.6%)	707 (37.4%)	359 (19.0%)
Patients with rheumatoid arthritis or juvenile arthritis [1] (%)	642 (46.5%)	672 (48.7%)	66 (0.5%)
Patients with rheumatoid arthritis [2] (%)	641 (46.6%)	668 (48.6%)	66 (0.5%)

[1] WHO ICD 10 codes M05, M06, M08 or M09. This group has been included in subsequent analyses.
[2] WHO ICD 10 codes M05 and M06.

10.2. Descriptive data

The characteristics of patients with a history of rheumatoid arthritis, including a prior history of neuropsychiatric events, is shown in Table 2. Follow-up time was different in the three groups. Tocilizumab had the longest and tofacitinib had the shortest mean follow-up time. Around 77-80% of patients in all three treatment groups were female with no significant differences between groups. The most frequent age group was 50-69 years in all three treatment groups. Patients in the tocilizumab group were significantly younger than in the two other groups. Around 10% of the patients in all three treatment groups had a neuropsychiatric history with no significant differences between groups, and the most frequent neuropsychiatric history was depression. Around 1% of patients had a history of

mood disorder with anxiety (WHO ICD 10 code F41). Most patients had received prior treatment with systemic corticosteroids and methotrexate, followed by NSAIDs, TNF-α blockers and leflunomide. Some differences were observed between the groups regarding prior treatment with minor tranquilizers, NSAIDs, systemic corticosteroids, sulfasalazine, methotrexate and TNF-α blockers.

Table 2 Characteristics of patients with rheumatoid arthritis initiating treatment with tofacitinib, baricitinib and tocilizumab

	All patients	Tofacitinib	Baricitinib	Tocilizumab
Total number of patients	1380	642	672	66
Mean follow-up time in years (SD) [1]	1.3 (0.8)	1.2 (0.8)	1.3 (0.8)	1.6 (0.7)
Maximum follow-up time in years	3.3	3.1	3.1	3.3
Female patients	1078 (78.1%)	505 (78.7%)	520 (77.4%)	53 (80.3%)
Male patients	302 (21.9%)	137 (21.3%)	152 (22.6%)	13 (19.7%)
Mean age in years (SD) [2]	61.7 (12.8)	61.9 (12.2)	62.0 (13.3)	56.1 (11.5)
Median age in years (IQR)	61 (54-71)	61 (54-71)	62 (54-73)	55 (51-63)
Age 18-49 years [3]	205 (14.9%)	87 (13.6%)	105 (15.6%)	13 (19.7%)
Age 50-69 years	795 (57.6%)	384 (59.8%)	365 (54.3%)	46 (69.7%)
Age **≥70** years	380 (27.5%)	171 (26.6%)	202 (30.1%)	7 (10.6%)
Any neuropsychiatric history	133 (9.6%)	64 (10.0%)	61 (9.1%)	8 (12.1%)
History of suicide or selfharm	4 (0.3%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
History of severe depression or bipolar disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of other depression	103 (7.5%)	49 (7.6%)	49 (7.3%)	5 (7.6%)
History of other mood disorder	23 (1.7%)	10 (1.6%)	13 (1.9%)	0 (0.0%)
History of other mood disorder: anxiety (F41 only)	16 (1.2%)	9 (1.4%)	7 (1.0%)	0 (0.0%)
History of other mood disorder (not F41)	8 (0.6%)	2 (0.3%)	6 (0.9%)	0 (0.0%)
Schizophrenia-related disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of psychoanaleptics (EphMRA ATC codes N06a and N06C)	19 (1.4%)	6 (0.9%)	10 (1.5%)	3 (4.5%)
History of minor tranquilizer (EphMRA ATC code N05 C) [4]	3 (0.2%)	2 (0.3%)	0 (0.0%)	1 (1.5%)
History of antipsychotics (EphMRA ATC code N05A)	3 (0.2%)	2 (0.3%)	1 (0.1%)	0 (0.0%)
Prior NSAID treatment [5]	736 (53.3%)	364 (56.7%)	329 (49.0%)	43 (65.2%)
Prior steroid treatment [6]	1196 (86.7%)	581 (90.5%)	558 (83.0%)	57 (86.4%)
Prior sulfasalazine treatment [7]	250 (18.1%)	138 (21.5%)	105 (15.6%)	7 (10.6%)
Prior methotrexate treatment [8]	1033 (74.9%)	511 (79.6%)	474 (70.5%)	48 (72.7%)
Prior azathioprine treatment	29 (2.1%)	11 (1.7%)	16 (2.4%)	2 (3.0%)
Prior leflunomide treatment	574 (41.6%)	283 (44.1%)	263 (39.1%)	28 (42.4%)
Prior hydroxychloroquine treatment	170 (12.3%)	86 (13.4%)	76 (11.3%)	8 (12.1%)
Prior **TNF-α** blocker treatment [9]	638 (46.2%)	308 (48.0%)	273 (40.6%)	57 (86.4%)

Comparisons that result in p values <0.05 are shown in bold. P values have not been corrected for multiple comparisons.

[1] P value for one-way Anova <0.0001. Mean follow-up time was significantly different in all three groups.

[2] P value for one-way Anova 0.0014. Mean age was significantly lower in the tocilizumab group compared to the tofacitinib group and the baricitinib group. There was no significant difference in mean age between tofacitinib and baricitinib.

[3] P value for age group by treatment group interaction 0.0034 (Fisher's exact test).

[4] P value for history of minor tranquilizer treatment by treatment group interaction 0.0376 (Fisher's exact test).

[5] P value for history of NSAID treatment by treatment group interaction 0.0027 (Fisher's exact test).

[6] P value for history of systemic corticosteroid treatment by treatment group interaction 0.0003 (Fisher's exact test).

[7] P value for history of sulfasalazine treatment by treatment group interaction 0.0064 (Fisher's exact test).

[8] P value for history of methotrexate treatment by treatment group interaction 0.0006 (Fisher's exact test).

[9] P value for history of TNF-α blocker treatment by treatment group interaction <0.0001 (Fisher's exact test).

10.3. Main results

10.3.1. Incidence of neuropsychiatric outcome events in patients with rheumatoid arthritis

A total of 46 patients had a neuropsychiatric outcome event during the follow-up period; 20 patients treated with tofacitinib, 24 patients treated with baricitinib and 2 patients treated with tocilizumab. Incidence rates of neuropsychiatric outcome events per 1000 person-years by prior history of neuropsychiatric events and treatment group are shown in Table 3. In patients with no history of neuropsychiatric events incidence rates were around 10-20 per 1000 person-years. As expected, rates were significantly higher, by about 5-10 times, in patients with a history of neuropsychiatric events compared to patients with no such history. There were no significant differences between tofacitinib, baricitinib or tocilizumab, but confidence intervals were wide. Depression and treatment with psychoanaleptics (EphMRA ATC codes N06A and N06C) were the most recorded neuropsychiatric outcome events. No suicide or self-harm events were recorded during the follow-up period. In patients with no prior history of neuropsychiatric events, other mood disorder with anxiety (WHO ICD 10 code F41) was not recorded during the follow-up period for tofacitinib or tocilizumab, whereas for baricitinib it was recorded at a rate of 1.2 per 1000 person-years.

Table 3 Incidence rates of neuropsychiatric events per 1000 person-years during the follow-up period

Incidence rate per 1000 P-Y (95% CI)						
	Patients without prior neuropsychiatric history (n=1247)			Patients with prior neuropsychiatric history (n=133)		
Event	Tofacitinib (n=578)	Baricitinib (n=611)	Tocilizumab (n=58)	Tofacitinib (n=64)	Baricitinib (n=61)	Tocilizumab (n=8)
Any neuropsychiatric outcome event	16.3 (8.1-29.2) (n=11)	19.7 (11.3-32.0) (n=16)	11.0 (0.3-61.5) (n=1)	117 (54.4-248) (n=9)	132 (56.8-259) (n=8)	84.0 (2.1-468) (n=1)
Suicide or self-harm	0.0 (0.0-5.5) (n=0)	0.0 (0.0-4.5) (n=0)	0.0 (0.0-40.7) (n=0)	0.0 (0.0-48.0) (n=0)	0.0 (0.0-60.7) (n=0)	0.0 (0.0-310) (n=0)
Severe depression or bipolar	0.0 (0.0-5.5) (n=0)	0.0 (0.0-4.5) (n=0)	0.0 (0.0-40.7) (n=0)	13.0 (0.3-72.5) (n=1)	0.0 (0.0-60.7) (n=0)	0.0 (0.0-310) (n=0)
Other depression	10.4 (4.2-21.4) (n=7)	7.4 (2.7-16.1) (n=6)	11.0 (0.3-61.5) (n=1)	91.1 (36.6-188) (n=7)	98.7 (36.2-215) (n=6)	84.0 (2.1-468) (n=1)
Other mood disorder	0.0 (0.0-5.5) (n=0)	3.7 (0.8-10.8) (n=3)	0.0 (0.0-40.7) (n=0)	26.0 (3.2-94.0) (n=2)	32.9 (4.0-119) (n=2)	0.0 (0.0-310) (n=0)
Anxiety (F41)	0.0 (0.0-5.5) (n=0)	1.2 (0.0-7.6) (n=1)	0.0 (0.0-40.7) (n=0)	26.0 (3.2-94.0) (n=2)	32.9 (4.0-119) (n=2)	0.0 (0.0-310) (n=0)
Other mood disorder (not F41)	0.0 (0.0-5.5) (n=0)	2.5 (0.3-8.9) (n=2)	0.0 (0.0-40.7) (n=0)	0.0 (0.0-48.0) (n=0)	0.0 (0.0-60.7) (n=0)	0.0 (0.0-310) (n=0)
Schizophrenia related	0.0 (0.0-5.5) (n=0)	1.2 (0.0-6.9) (n=1)	0.0 (0.0-40.7) (n=0)	0.0 (0.0-48.0) (n=0)	0.0 (0.0-60.7) (n=0)	0.0 (0.0-310) (n=0)
Treatment with N06A or N06C	8.9 (3.3-19.4) (n=6)	11.1 (5.1-21.0) (n=9)	0.0 (0.0-40.7) (n=0)	0.0 (0.0-48.0) (n=0)	65.8 (17.9-168) (n=4)	0.0 (0.0-310) (n=0)
Treatment with N05C	3.0 (0.4-10.7) (n=2)	0.0 (0.0-4.5) (n=0)	0.0 (0.0-40.7) (n=0)	0.0 (0.0-48.0) (n=0)	0.0 (0.0-60.7) (n=0)	0.0 (0.0-310) (n=0)
Treatment with N05A	1.5 (0.0-8.3) (n=1)	2.5 (0.3-8.9) (n=2)	0.0 (0.0-40.7) (n=0)	0.0 (0.0-48.0) (n=0)	0.0 (0.0-60.7) (n=0)	0.0 (0.0-310) (n=0)

10.3.2. Comparison between rheumatoid arthritis patients that did and those that did not experience neuropsychiatric outcome events during the follow-up period

A comparison between patients that did and patients that did not experience neuropsychiatric outcome events is shown in Table 4 for all patients with rheumatoid arthritis and in Table 5 for the subgroup of patients that had no prior neuropsychiatric history. There was no difference in the gender distribution whereas the age distribution was somewhat skewed towards lower ages in patients that experienced neuropsychiatric outcome events during the follow-up period compared to patients that did not experience such events, although there was no significant difference in mean age. In the analysis restricted to patients with no prior neuropsychiatric history there was no significant difference in age. In all patients with rheumatoid arthritis fewer patients with neuropsychiatric outcome events vs. those without outcome events had a history of treatment with sulfasalazine whereas no significant differences were identified as regards prior or concomitant treatment with NSAIDs, systemic corticosteroids, methotrexate, azathioprine, leflunomide, hydroxychloroquine or TNF-α blockers. There was also no significant difference in mean number of days between the first and the last prescription. Among patients with no neuropsychiatric history, prior NSAID treatment was less common in patients that experienced neuropsychiatric outcome events than in patients that did not experience neuropsychiatric outcome events.

Table 4 Comparison between patients that did and patients that did not experience neuropsychiatric outcome events – all patients with rheumatoid arthritis

Patient characteristics	Patients with neuropsychiatric outcome event (n=46)	Patients without neuropsychiatric outcome event (n=1334)
Female patients	37 (80.4%)	1041 (78.0%)
Male patients	9 (19.6%)	293 (22.0%)
Mean number of days between first and last prescription (SD)	452.9 (261.8)	400.1 (272.4)
Median number of days between first and last prescription (IQR)	405 (252-531)	365 (190-541)
Mean age in years (SD)	58.1 (12.1)	61.8 (12.8)
Median age in years (IQR)	57 (49-65)	61 (54-71)
Age 18-49 years [1]	13 (28.3%)	192 (14.4%)
Age 50-69 years	25 (54.3%)	770 (57.7%)
Age **≥70** years	8 (17.4%)	372 (27.9%)
Prior NSAID treatment	21 (45.7%)	715 (53.6%)
Prior steroid treatment	40 (87.0%)	1156 (86.7%)
Prior sulfasalazine treatment [2]	3 (6.5%)	247 (18.5%)
Prior methotrexate treatment	36 (78.3%)	997 (74.7%)
Prior azathioprine treatment	0 (0.0%)	29 (2.2%)
Prior leflunomide treatment	17 (37.0%)	557 (41.8%)
Prior hydroxychloroquine treatment	8 (17.4%)	162 (12.1%)
Prior TNF-α blocker treatment	17 (37.0%)	621 (46.6%)
Concomitant NSAID treatment	16 (34.8%)	386 (28.9%)
Concomitant steroid treatment	32 (69.6%)	885 (66.3%)
Concomitant sulfasalazine treatment	2 (4.3%)	19 (1.4%)
Concomitant methotrexate treatment	22 (47.8%)	529 (39.7%)
Concomitant azathioprine treatment	0 (0.0%)	5 (0.4%)
Concomitant leflunomide treatment	1 (2.2%)	45 (3.4%)
Concomitant hydroxychloroquine treatment	1 (2.2%)	23 (1.7%)
Concomitant TNF-α blocker treatment	5 (10.9%)	154 (11.5%)

Comparisons that result in p values <0.05 are shown in bold. P values have not been corrected for multiple comparisons.

[1] P value for age group by outcome interaction 0.0319 (Fisher's exact test).

[2] P value for history of sulfasalazine treatment by outcome interaction 0.0486 (Fisher's exact test).

Table 5 Comparison between patients with rheumatoid arthritis and no neuropsychiatric history that did and did not experience neuropsychiatric outcome events

	Patients with neuropsychiatric outcome event (n=28)	Patients without neuropsychiatric outcome event (n=1219)
Female patients	21 (75.0%)	936 (76.8%)
Male patients	7 (25.0%)	283 (23.2%)
Mean number of days between first and last prescription (SD)	452.9 (255.8)	403.3 (273.9)
Median number of days between first and last prescription (IQR)	422.5 (239-554)	365 (191-552)
Mean age in years (SD)	58.3 (11.5)	61.9 (12.9)
Median age in years (IQR)	57 (50-67)	62 (54-72)
Age 18-49 years	6 (21.4%)	178 (14.6%)
Age 50-69 years	16 (57.1%)	693 (56.8%)
Age ≥70 years	6 (21.4%)	348 (28.6%)
Prior NSAID treatment [1]	9 (32.1%)	639 (52.4%)
Prior steroid treatment	25 (89.3%)	1053 (86.4%)
Prior sulfasalazine treatment	2 (7.1%)	223 (18.3%)
Prior methotrexate treatment	23 (82.1%)	907 (74.4%)
Prior azathioprine treatment	0 (0.0%)	25 (2.1%)
Prior leflunomide treatment	10 (35.7%)	503 (41.3%)
Prior hydroxychloroquine treatment	4 (14.3%)	144 (11.8%)
Prior TNF-α blocker treatment	12 (42.9%)	567 (46.5%)
Concomitant NSAID treatment	6 (21.4%)	343 (28.1%)
Concomitant steroid treatment	19 (67.9%)	806 (66.1%)
Concomitant sulfasalazine treatment	2 (7.1%)	16 (1.3%)
Concomitant methotrexate treatment	13 (46.4%)	486 (39.9%)
Concomitant azathioprine treatment	0 (0.0%)	4 (0.3%)
Concomitant leflunomide treatment	0 (0.0%)	44 (3.6%)
Concomitant hydroxychloroquine treatment	0 (0.0%)	18 (1.5%)
Concomitant TNF-α blocker treatment	4 (14.3%)	139 (11.4%)

Comparisons that result in p values <0.05 are shown in bold. P values have not been corrected for multiple comparisons.

[1] P value for history of NSAID treatment by outcome interaction 0.0364 (Fisher's exact test).

10.4. Post hoc analyses

10.4.1. All patients initiating treatment with tofacitinib, baricitinib and tocilizumab

Post hoc analyses were also performed including all patients initiating treatment with tofacitinib, baricitinib and tocilizumab because of the limited number of patients with a prior diagnosis of rheumatoid arthritis treated with tocilizumab.

For the characteristics of all patients, please see Table S1 in Annex 4. Incidence rates of neuropsychiatric outcome events, in patients with vs. patients without a history of such events, were still similar when all patients were considered regardless of indication (Table S2 in Annex 3).

There was also still no significant difference between genders when patients with and patients without neuropsychiatric outcome events were compared, and patients with neuropsychiatric outcome events were again younger than patients without such events (Table S3 in Annex 3). Again, a difference in age was also not observed when the analysis was restricted to patients with no history of neuropsychiatric events (Table S4 in Annex 3).

Among patients with no history of neuropsychiatric events prior NSAID treatment was again less common in patients with neuropsychiatric outcome events compared to patients without such events. When all patients with outcome events were compared to patients without outcome events, prior sulfasalazine treatment was also again less common in patients with compared to patients without neuropsychiatric outcome events. This analysis also identified prior TNF-α blocker treatment as less common in patients with vs. patients without neuropsychiatric outcome events.

10.4.2. Survival curves for neuropsychiatric outcome events

Survival curves for the different neuropsychiatric outcome events in the three treatment groups are shown in Annex 2. There were no significant differences between the groups.

11. Discussion

11.1. Main results

The incidence rate of neuropsychiatric events in patients with rheumatoid arthritis with no prior history of such events was around 10-20 per 1000 person-years of follow-up after treatment initiation. Incidence rates were significantly higher in patients with a prior history of neuropsychiatric events. No difference in incidence rates for neuropsychiatric events was identified between tofacitinib, baricitinib and tocilizumab, but confidence limits were wide, and the analyses are based on small event numbers. Depression and treatment with psychoanaleptics were the most observed neuropsychiatric outcome events.

Patients with neuropsychiatric outcome events were younger than patients without such events, but a difference in the age distribution could only be observed in patients with a history of neuropsychiatric events, and not in patients that had no such history. Prior treatments for rheumatoid arthritis are likely to be intricately linked to the severity of the disease. In all patients with rheumatoid arthritis patients with neuropsychiatric outcome events were less likely to have received prior treatment with sulfasalazine compared to patients without neuropsychiatric outcome events. Furthermore, in patients with no history of neuropsychiatric events, patients with compared to patients without neuropsychiatric outcome events were less likely to have prior treatment with NSAIDS. However, these observations are based on a small group of patients and are related to a low number of events.

The number of patients included in the study was insufficient to be able to compare the incidence of neuropsychiatric outcome events between treatment groups, and even more so when individual neuropsychiatric outcome events are considered.

The duration of follow-up was restricted to a maximum of 365 days after the last prescription and allowing for a maximum gap between prescriptions of 365 days. On the other hand, further available follow-up time in the rheumatoid arthritis population, after the end of observation in the study is limited, adding a maximum of 5.5% to the observation time in the study for all three treatments (3.2 and 3.9% for tofacitinib and baricitinib and 37.0% for tocilizumab). It therefore seems unlikely that extending the follow-up time will significantly change the results.

11.2. Limitations

The main limitations are the limited number of patients studied in combination with an infrequent outcome event, and possible incompleteness of recording of confounding factors and outcome events.

Recording of psychiatric events might be incomplete as the patient may consult another physician or specialist or may be hospitalised for the event, which may or may not be recorded by the treating physician.

The occurrence of psychiatric events is known to be higher in patients with rheumatoid arthritis compared to the general population. This study provides incidence rates of psychiatric events in patients treated with tofacitinib, baricitinib or tocilizumab, with and without a psychiatric history. A comparative cohort study of the causal relationship between the treatment and the occurrence of psychiatric events adjusting for relevant covariates was not considered possible due to the limited size of the treated population and the small number of outcome events. Stratification by severity of indication was also not addressed as part of the foreseen descriptive analyses.

In Germany the patient has free physician choice: in IMS® Disease Analyzer Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians

concurrently, collected data may be incomplete. The analysis is therefore restricted to patients overseen by internal medicines specialists. However, it cannot be excluded that the patient is seen by GPs or psychiatrists who prescribe or document diagnosis of psychiatric events and capturing of these outcome data might therefore be incomplete.

11.3. Interpretation

The study size was too small to be able to adequately compare incidence rates of neuropsychiatric events between tofacitinib, baricitinib and tocilizumab. Results are mainly descriptive and stratified by a prior history of neuropsychiatric events. No further adjustments were made. For this reason, the study can only provide limited information in how far the risk of neuropsychiatric events could differ between the treatments. Overall, incidence rates between the three treatment groups are similar, but differences cannot be excluded. Due to the limitations in study size and lack of adjustment for confounding it is also not possible to compare incidence rates of individual neuropsychiatric outcome events between treatment groups.

12. Summary and conclusion

This descriptive cohort study evaluated the incident use baricitinib, tofacitinib or tocilizumab from January 2017 to June 2020 within adult patients with rheumatoid arthritis seen at internal medicine specialists recorded within the IMS® Disease Analyzer Germany database. The study included 825 patients receiving tofacitinib while 707 patients receiving baricitinib and 359 were treated with tocilizumab. The majority (77-80%) of patients were female and treatment was most prominent in the age group of 50-69 years. The majority of patients treated did not have a recorded neuropsychiatric history (recorded in 9.6% of patients). Neuropsychiatric outcomes after treatment initiation were recorded in 20 patients treated with tofacitinib, 24 patients treated with baricitinib and 2 patients treated with tocilizumab. Depression and treatment with psychoanaleptics (EphMRA ATC codes N06A and N06C) were the most recorded neuropsychiatric outcome events. No suicide or self-harm events were recorded during the follow-up period. The incidence rates of neuropsychiatric events in patients without prior neuropsychiatric events were 16.3 (95% CI:8.1-29.2) per 100.000 patient-years in patients receiving tofacitinib, 19.7 (95% CI 11.3-32.0) per 100.000 patient-years in patients receiving baricitinib as well as 11.0 (95% CI: 0.3-61.5) in patients receiving tocilizumab. Incidence rates were higher in patients with prior neuropsychiatric history with point estimates ranging from 84-132 events per 100.000 patient years.

The results show that neuropsychiatric events occur in adult patients with rheumatoid arthritis newly treated with tofacitinib, baricitinib and tocilizumab. Event rated tend to be higher in patients with prior neuropsychiatric events. The results of this analysis are based on a small sample of patients, are purely descriptive without adjustment for confounding and therefore need to be interpreted cautiously.

13. References

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14. Comments received on draft analysis plan

MS 1

According to conclusion of the last PSUSA for upadacitinib.

„ During assessment of this PSUR, a signal was confirmed for another JAK inhibitor tofacitinib regarding psychiatric adverse reactions (anxiety, suicidal ideation). This signal does not seem to be clear class signal for all JAK-inhibitors. For upadacitinib, there are not enough data in this PSUR regarding this issue which would allow proper assessment and conclusion to be made. However, *this issue will be analyzed and assessed in next PSUR (submission date: 24.10.2020)*.„

There are cases in Eudravigilance. Maybe, upadactinib should be also included in analysis.

EMA Comment

Upadactinib was – alongside other JAK inhibitors included in the Feasibility Analysis (Please see section Annex 4 Feasibility Feedback). The number of patients recorded in the databases was very low and there were no cases recorded for updactinib in the databases. Therefore, inclusion of this substance in the analysis might not lead to meaningful results. Such an analysis could be repeated at a later stage, if more exposure has been accrued in the databases. For the time being, the substance is however not included in the analysis.

MS 2

In general, we endorse the proposed protocol. If feasible, it could be worthwhile to complete the information collected about the psychiatric history with the collection of data on prescription of drugs

associated with such events (e.g. ATC groups N05B - Anxiolytics, N05C - Hypnotics and sedatives, and N06 PSYCHOANALEPTICS)

EMA Comment

The analysis plan has been updated to include the prescribing of drugs for psychiatric treatment (WHO ATC groups N05A, N05B, N06A and N06C corresponding to EphMRA ATC groups N5A, N5C, N06A and N06C).

Instead of including the full coverage of drugs falling under N06, we will focus on drugs pertaining to N06A (Antidepressants) and N06C (Psycholeptics and psychoanaleptics in combination) and will not include N06B (Psychostimulants, agents used for ADHD and Nootropics) and N06D (Anti-dementia Drugs) as these are considered to be not specific enough.

Please note that the amendments pertain to both considering prescribing as an outcome as well as considering prescribing of these drugs as part of the psychiatric history within 365 days prior to first prescribing of the tofacitinib, baricitinib or tocilizumab.

Please also note that the databases used within the analysis are using the EPhMRA classification, which is not necessarily mapping with the WHO ATC Code classificatioin (WHO is substance based, EPhMRA is product-based). We have therefore also included an Annex listing the substances under the corresponding EPhMRA ATC codes (see Annex 1).

15. Annexes

Annex 1: List of products

Annex 2: Survival curves for different neuropsychiatric events by treatment group

Annex 3: Results of analyses in all incident patients initiating treatment with tofacitinib, baricitinib and tocilizumab

Annex 4: Feasibility Feedback

Annex 1 List of products

Products containing tofacitinib

Product number	Product name
GE5372965	XELJANZ CC4>> FILMTABL 10MG 56 (N2)
GE16545154	XELJANZ FILMTABL 5MG 56 (N2)
GE16722895	XELJANZ FILMTABL 5MG 182 (N3)
GE16795558	XELJANZ CC4>> FILMTABL 5MG 56 (N2)
GE17162177	XELJANZ AB8>> FILMTABL 5MG 56 (N2)
GE17462394	XELJANZ P5V>> FILMTABL 5MG 56 (N2)
GE17475623	XELJANZ KHP>> FILMTABL 5MG 56 (N2)
GE17622923	XELJANZ FILMTABL 10MG 182 (N3)
GE17710154	XELJANZ FILMTABL 10MG 112
GE17775709	XELJANZ FILMTABL 10MG 56 (N2)
GE17846890	XELJANZ KHP>> FILMTABL 5MG 182 (N3)
GE17951412	XELJANZ A4X>> FILMTABL 5MG 56 (N2)
GE17952419	XELJANZ KHP>> FILMTABL 10MG 56 (N2)
GE18200199	XELJANZ A4X>> FILMTABL 5MG 182 (N3)
GE18247256	XELJANZ AB8>> FILMTABL 5MG 182 (N3)
GE18346281	XELJANZ EU0>> FILMTABL 5MG 56 (N2)
GE18470346	XELJANZ ORI>> FILMTABL 5MG 56 (N2)
GE18499061	XELJANZ EUP>> FILMTABL 5MG 56 (N2)
GE18871517	XELJANZ ORI>> FILMTABL 5MG 182 (N3)
GE18965562	XELJANZ HM2>> FILMTABL 5MG 56 (N2)
GE18971664	XELJANZ P5V>> FILMTABL 10MG 56 (N2)
GE18995623	XELJANZ EUP>> FILMTABL 10MG 56 (N2)
GE19007911	XELJANZ AB8>> FILMTABL 10MG 56 (N2)
GE19604915	XELJANZ FILMTABL RET 11MG 91 (N3)
GE19607644	XELJANZ FILMTABL RET 11MG 28 (N2)

Products containing baricitinib

Product number	Product name
GE16437187	OLUMIANT FILMTABL 4MG 28 (N1)
GE16443545	OLUMIANT FILMTABL 2MG 28 (N1)
GE16467424	OLUMIANT FILMTABL 2MG 98 (N3)
GE16505765	OLUMIANT FILMTABL 4MG 98 (N3)
GE17381297	OLUMIANT HM2>> FILMTABL 4MG 98 (N3)
GE17414728	OLUMIANT HM2>> FILMTABL 2MG 98 (N3)
GE17454194	OLUMIANT AB8>> FILMTABL 4MG 28 (N1)
GE17520054	OLUMIANT HM2>> FILMTABL 4MG 28 (N1)
GE17706271	OLUMIANT CC4>> FILMTABL 4MG 98 (N3)
GE17771071	OLUMIANT AB8>> FILMTABL 2MG 28 (N1)
GE17803389	OLUMIANT KHP>> FILMTABL 4MG 98 (N3)
GE17881403	OLUMIANT KHP>> FILMTABL 2MG 28 (N1)
GE17963394	OLUMIANT CC4>> FILMTABL 2MG 28 (N1)
GE17971827	OLUMIANT AB8>> FILMTABL 4MG 98 (N3)
GE18037616	OLUMIANT KHP>> FILMTABL 4MG 28 (N1)
GE18205211	OLUMIANT KHP>> FILMTABL 2MG 98 (N3)
GE18244201	OLUMIANT AB8>> FILMTABL 2MG 98 (N3)
GE18465183	OLUMIANT ORI>> FILMTABL 2MG 98 (N3)
GE18495807	OLUMIANT P5V>> FILMTABL 2MG 28 (N1)
GE18748920	OLUMIANT ORI>> FILMTABL 4MG 98 (N3)
GE18796049	OLUMIANT ORI>> FILMTABL 2MG 28 (N1)
GE18816806	OLUMIANT A4X>> FILMTABL 4MG 98 (N3)
GE18825380	OLUMIANT CC4>> FILMTABL 2MG 98 (N3)
GE18837227	OLUMIANT CC4>> FILMTABL 4MG 28 (N1)
GE19015049	OLUMIANT P5V>> FILMTABL 4MG 98 (N3)
GE19331091	OLUMIANT P5V>> FILMTABL 2MG 98 (N3)
GE19507321	OLUMIANT EUP>> FILMTABL 2MG 28 (N1)
GE19712966	OLUMIANT FILMTABL KVA 4MG ALT 28

Products containing tocilizumab

Product number	Product name
GE8204698	ROACTEMRA INF LSG FL 400MG KONZ 20ML (N1)
GE8209090	ROACTEMRA INF LSG FL 80MG KONZ 4ML (N1)
GE8218134	ROACTEMRA INF LSG FL 400MG KONZ 4 20ML (N2)
GE8226643	ROACTEMRA INF LSG FL 200MG KONZ 10ML (N1)
GE8247594	ROACTEMRA INF LSG FL 80MG KONZ 4 4ML (N2)
GE8261757	ROACTEMRA INF LSG FL 200MG KONZ 4 10ML (N2)
GE9032382	ROACTEMRA CC4>> INF LSG FL 80MG KONZ 4ML (N1)
GE9120156	ROACTEMRA CC4>> INF LSG FL 200MG KONZ 10ML (N1)
GE9125563	ROACTEMRA CC4>> INF LSG FL 400MG KONZ 20ML (N1)
GE9718386	ROACTEMRA HM2>> INF LSG FL 400MG KONZ 20ML (N1)
GE10130859	ROACTEMRA HM2>> INF LSG FL 200MG KONZ 10ML (N1)
GE10156153	ROACTEMRA HM2>> INF LSG FL 80MG KONZ 4ML (N1)
GE10189754	ROACTEMRA ORI>> INF LSG FL 400MG KONZ 20ML (N1)
GE10493495	ROACTEMRA CC4>> INF LSG FL 80MG KONZ 4 4ML (N2)
GE11757556	ROACTEMRA EUP>> INF LSG FL 400MG KONZ 20ML (N1)
GE11840283	ROACTEMRA KHP>> INF LSG FL 80MG KONZ 4ML (N1)
GE11996746	ROACTEMRA CC4>> INF LSG FL 400MG KONZ 4 20ML (N2)
GE12291096	ROACTEMRA KHP>> INF LSG FL 400MG KONZ 20ML (N1)
GE12296169	ROACTEMRA KHP>> INF LSG FL 80MG KONZ 4 4ML (N2)
GE12302848	ROACTEMRA AC9>> INF LSG FL 400MG KONZ 20ML (N1)
GE12412890	ROACTEMRA EUP>> INF LSG FL 80MG KONZ 4ML (N1)
GE12443427	ROACTEMRA I1P>> INF LSG FL 400MG KONZ 20ML (N1)
GE12495594	ROACTEMRA GRK>> INF LSG FL 200MG KONZ 10ML (N1)
GE12577640	ROACTEMRA EUP>> INF LSG FL 200MG KONZ 10ML (N1)
GE12589497	ROACTEMRA ML8>> INF LSG FL 400MG KONZ 20ML (N1)
GE12838131	ROACTEMRA ML8>> INF LSG FL 80MG KONZ 4ML (N1)
GE13047963	ROACTEMRA ML8>> INF LSG FL 200MG KONZ 10ML (N1)
GE13841176	ROACTEMRA BRA>> INF LSG FL 80MG KONZ 4ML (N1)
GE14131353	ROACTEMRA FERT.SPR.S.C 162MG 4 .9ML (N2)
GE8204698	ROACTEMRA INF LSG FL 400MG KONZ 20ML (N1)
GE8209090	ROACTEMRA INF LSG FL 80MG KONZ 4ML (N1)
GE8218134	ROACTEMRA INF LSG FL 400MG KONZ 4 20ML (N2)
GE8226643	ROACTEMRA INF LSG FL 200MG KONZ 10ML (N1)
GE8247594	ROACTEMRA INF LSG FL 80MG KONZ 4 4ML (N2)
GE8261757	ROACTEMRA INF LSG FL 200MG KONZ 4 10ML (N2)
GE9032382	ROACTEMRA CC4>> INF LSG FL 80MG KONZ 4ML (N1)
GE9120156	ROACTEMRA CC4>> INF LSG FL 200MG KONZ 10ML (N1)
GE9125563	ROACTEMRA CC4>> INF LSG FL 400MG KONZ 20ML (N1)
GE9718386	ROACTEMRA HM2>> INF LSG FL 400MG KONZ 20ML (N1)
GE10130859	ROACTEMRA HM2>> INF LSG FL 200MG KONZ 10ML (N1)
GE10156153	ROACTEMRA HM2>> INF LSG FL 80MG KONZ 4ML (N1)
GE10189754	ROACTEMRA ORI>> INF LSG FL 400MG KONZ 20ML (N1)
GE10493495	ROACTEMRA CC4>> INF LSG FL 80MG KONZ 4 4ML (N2)
GE11757556	ROACTEMRA EUP>> INF LSG FL 400MG KONZ 20ML (N1)

Product number	Product name
GE15765626	ROACTEMRA EU0>> INF LSG FL 80MG KONZ 4ML (N1)
GE15831489	ROACTEMRA AXV>> INF LSG FL 400MG KONZ 20ML (N1)
GE15860931	ROACTEMRA AXV>> INF LSG FL 200MG KONZ 10ML (N1)
GE15861582	ROACTEMRA AB8>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE15863378	ROACTEMRA CH4>> INF LSG FL 400MG KONZ 4 20ML (N2)
GE15921018	ROACTEMRA AXV>> INF LSG FL 200MG KONZ 4 10ML (N2)
GE15997348	ROACTEMRA EUP>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE16046915	ROACTEMRA AB8>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE16090746	ROACTEMRA AXV>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE16121427	ROACTEMRA E-M>> INF LSG FL 400MG KONZ 20ML (N1)
GE16187703	ROACTEMRA E-M>> INF L.FL.ALT 80MG KONZ 4ML (N1)
GE16187880	ROACTEMRA EU0>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE16187904	ROACTEMRA CH4>> INF LSG FL 80MG KONZ 4ML (N1)
GE16187908	ROACTEMRA E-M>> INF L.FL.ALT 400MG KONZ 20ML (N1)
GE16188010	ROACTEMRA BRA>> INF LSG FL 200MG KONZ 10ML (N1)
GE16188015	ROACTEMRA EU0>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE16241182	ROACTEMRA MPM>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE16352506	ROACTEMRA ORI>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE16443346	ROACTEMRA EUP>> INF LSG FL 400MG KONZ 4 20ML (N2)
GE16446073	ROACTEMRA HM2>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE16499310	ROACTEMRA ORI>> PEN 162MG 4 .9ML (N2)
GE16579862	ROACTEMRA AB8>> INF LSG FL 200MG KONZ 10ML (N1)
GE16597983	ROACTEMRA HM2>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE16633872	ROACTEMRA AXV>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE16636262	ROACTEMRA AC9>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE16636784	ROACTEMRA AB8>> INF LSG FL 80MG KONZ 4ML (N1)
GE16884567	ROACTEMRA AC9>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE17091744	ROACTEMRA P5V>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE17117713	ROACTEMRA AB8>> INF LSG FL 400MG KONZ 20ML (N1)
GE17168643	ROACTEMRA KHP>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE17365069	ROACTEMRA PEN 162MG 12 .9ML (N3)
GE17386397	ROACTEMRA AXV>> INF LSG FL 80MG KONZ 4 4ML (N2)
GE17400725	ROACTEMRA PEN 162MG 4 .9ML (N2)
GE17530182	ROACTEMRA EUP>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE17600622	ROACTEMRA ER4>> FERT.SPR.S.C 162MG 4 .9ML (N2)
GE18161567	ROACTEMRA BBF>> INF LSG FL 400MG KONZ 4 20ML (N2)
GE18193747	ROACTEMRA E-M>> INF LSG FL 80MG KONZ 4ML (N1)
GE18198728	ROACTEMRA EU0>> INF LSG FL 400MG KONZ 20ML (N1)
GE18247919	ROACTEMRA P5V>> INF LSG FL 400MG KONZ 20ML (N1)
GE18368702	ROACTEMRA KHP>> PEN 162MG 4 .9ML (N2)
GE18414826	ROACTEMRA I1P>> INF LSG FL 80MG KONZ 4ML (N1)
GE18479975	ROACTEMRA KHP>> PEN 162MG 12 .9ML (N3)
GE18749693	ROACTEMRA CH4>> PEN 162MG 12 .9ML (N3)
GE18798498	ROACTEMRA P5V>> INF LSG FL 200MG KONZ 4 10ML (N2)
GE18843723	ROACTEMRA AXV>> INF LSG FL 80MG KONZ 4ML (N1)

Product number	Product name
GE18939354	ROACTEMRA EUP>> PEN 162MG 4 .9ML (N2)
GE18945314	ROACTEMRA P5V>> PEN 162MG 4 .9ML (N2)
GE19005815	ROACTEMRA P5V>> FERT.SPR.S.C 162MG 12 .9ML (N3)
GE19041834	ROACTEMRA AB8>> PEN 162MG 12 .9ML (N3)
GE19043021	ROACTEMRA CH4>> INF LSG FL 200MG KONZ 10ML (N1)
GE19043022	ROACTEMRA CH4>> INF LSG FL 400MG KONZ 20ML (N1)
GE19533499	ROACTEMRA AXV>> PEN 162MG 12 .9ML (N3)
GE19589095	ROACTEMRA CC4>> PEN 162MG 12 .9ML (N3)
GE19607952	ROACTEMRA P5V>> PEN 162MG 12 .9ML (N3)
GE19617702	ROACTEMRA CC4>> PEN 162MG 4 .9ML (N2)
GE19695347	ROACTEMRA CH4>> INF LSG FL 200MG KONZ 4 10ML (N2)

Annex 2 Survival curves for the different neuropsychiatric outcome events in patients initiating treatment with tofacitinib, baricitinib and tocilizumab

In all figures, the x axis shows the follow-up time in days and the y axis shows the probability of remaining free of neuropsychiatric outcome event.

Figure 1 Survival curves for all outcome events (n=46) by treatment group

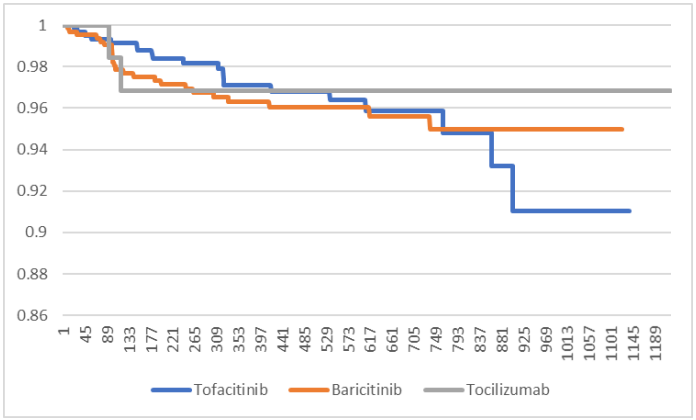


Figure 2 Survival curves for all outcome events (n=28) in patients with no neuropsychiatric history by treatment group

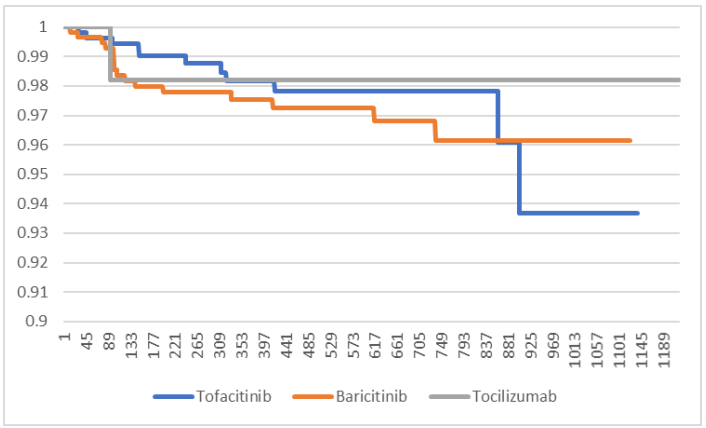


Figure 3 Survival curves for all outcome events (n=18) in patients with neuropsychiatric history by treatment group

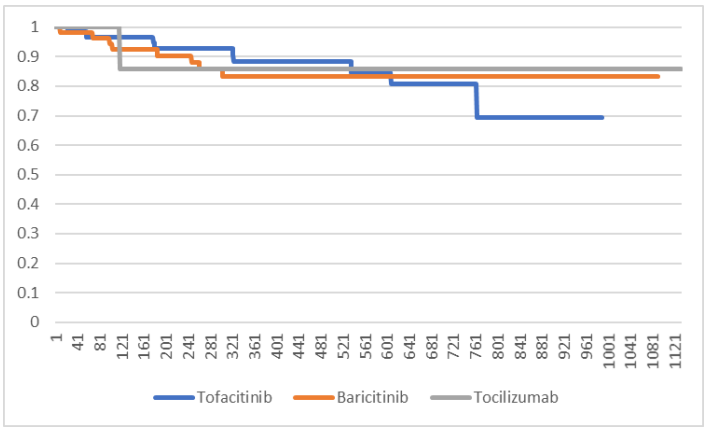


Figure 4 Survival curves for severe depression/bipolar disease (n=1) by treatment group

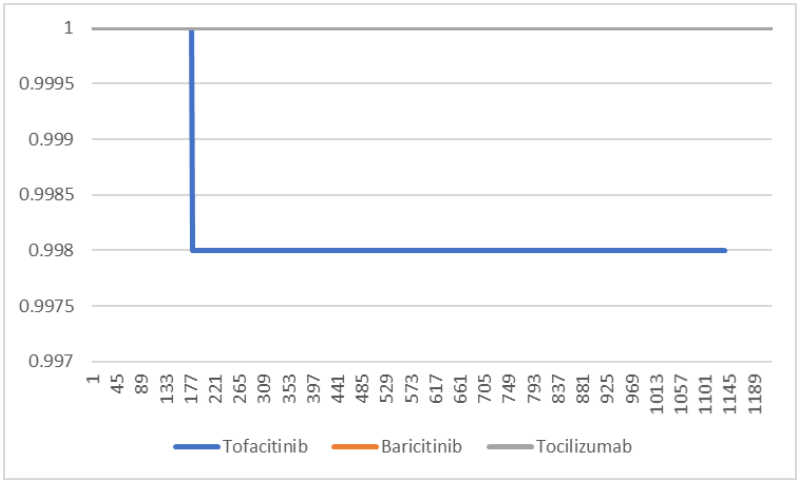


Figure 5 Survival curves for other depression (n=28) by treatment group

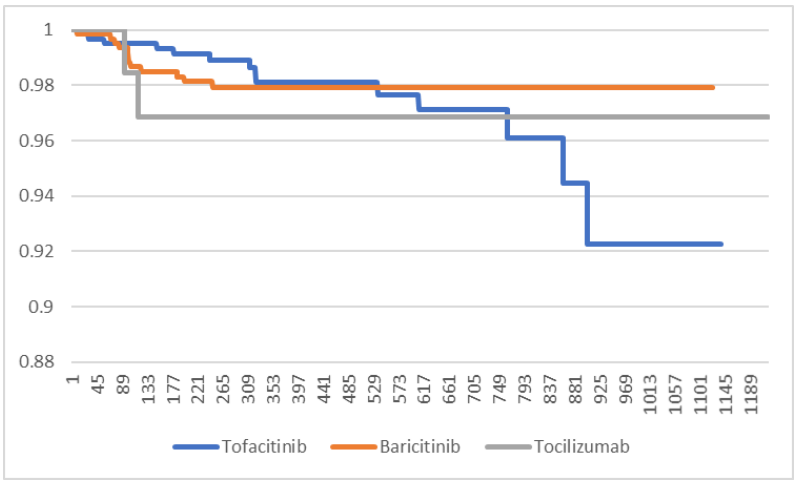


Figure 6 Survival curves for other mood disorders (n=7) by treatment group

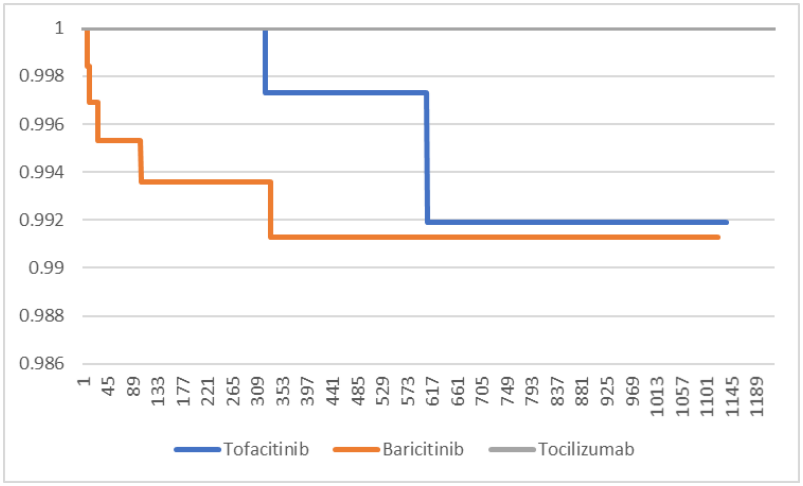


Figure 7 Survival curves for anxiety mood disorders (n=5) by treatment group: ICD 10 code F41

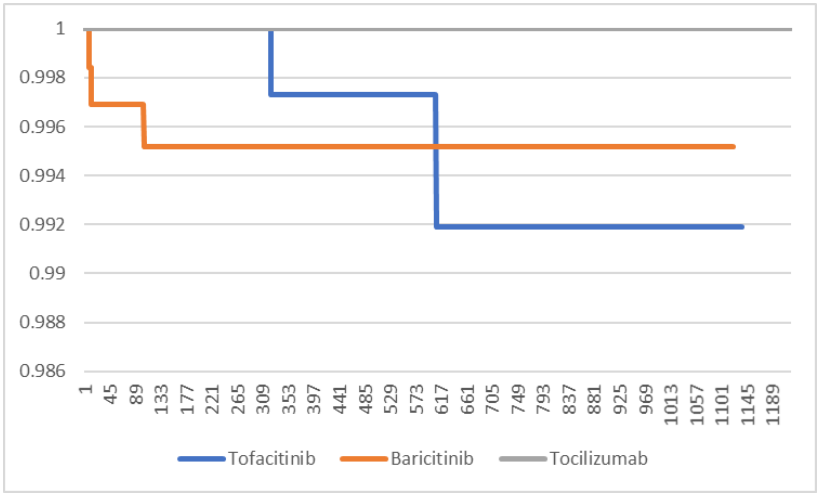


Figure 8 Survival curves for other mood disorders except ICD 10 code F41 (n=2) by treatment group

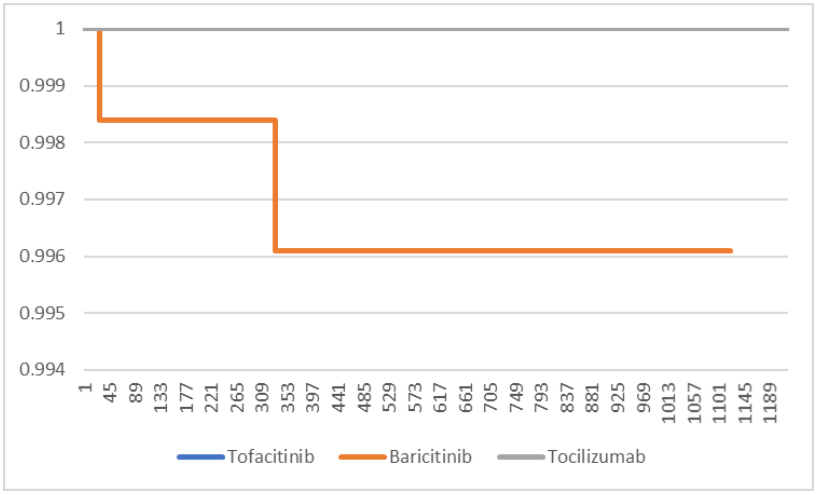


Figure 9 Survival curves for schizophrenia-related disorders (n=1) by treatment group

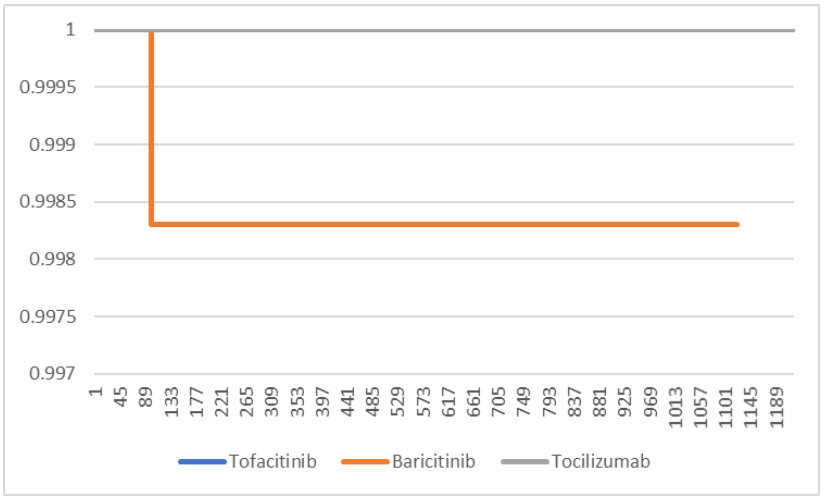


Figure 10 Survival curves for psychoanaleptic treatment (EphMRA ATC codes N06A and N06C) (n=19) by treatment group

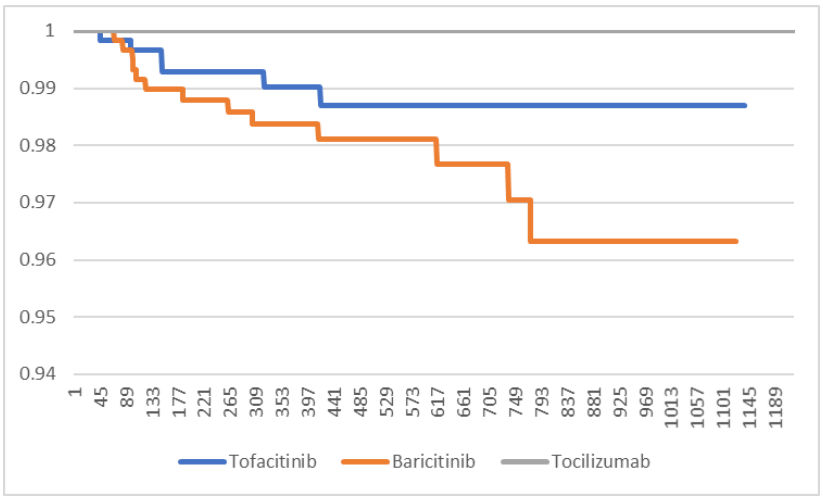


Figure 11 Survival curves for treatment with minor tranquilizers (EphMRA ATC code N05C) (n=2) by treatment group

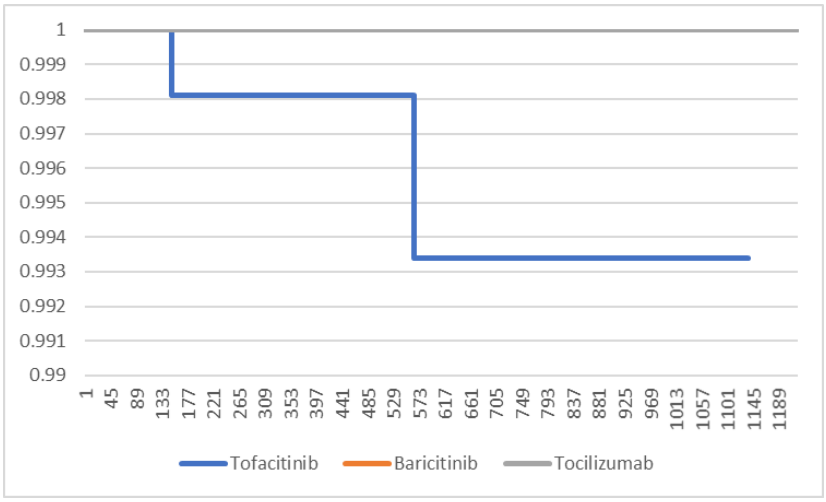
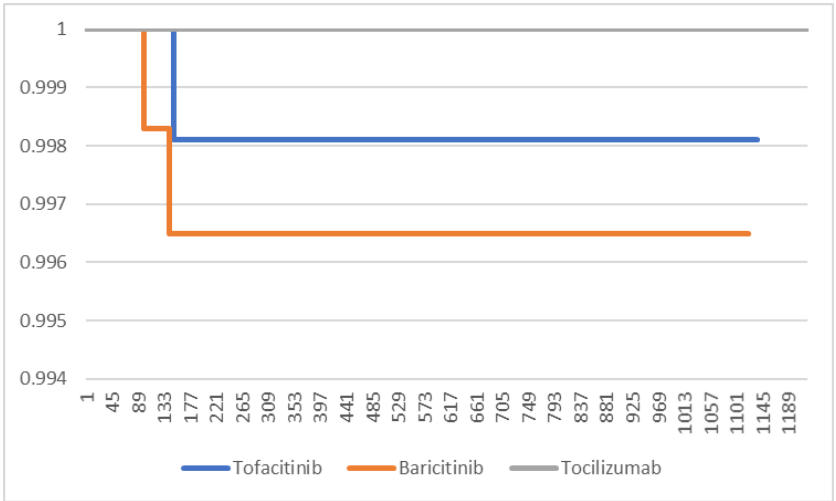


Figure 12 Survival curves for antipsychotic treatment (EphMRA ATC code N05A) (n=3) by treatment group



Annex 3 Results of analyses in all incident patients initiating treatment with tofacitinib, baricitinib and tocilizumab

Table S 1 Characteristics of all incident patients initiating treatment with tofacitinib, baricitinib and tocilizumab

	All patients	Tofacitinib	Baricitinib	Tocilizumab
Total number of patients	1891	825	707	359
Mean follow-up time in years (SD) [1]	1.3 (0.8)	1.1 (0.7)	1.3 (0.8)	1.5 (0.9)
Maximum follow-up time in years	3.4	3.1	3.1	3.4
Female patients	1425 (75.4%)	610 (73.0%)	546 (77.2%)	269 (74.9%)
Male patients	466 (24.6%)	215 (26.1%)	161 (22.8%)	90 (25.1%)
Mean age in years (SD) [2]	60.4 (13.4)	59.2 (13.5)	62.0 (13.2)	59.9 (13.5)
Median age in years (IQR)	61 (53-70)	61 (53-70)	62 (55-73)	59 (51-68)
Age 18-49 years [3]	337 (17.8%)	167 (20.2%)	108 (15.3%)	62 (17.3%)
Age 50-69 years	1071 (56.6%)	477 (57.8%)	387 (54.7%)	207 (57.7%)
Age **≥70** years	483 (25.5%)	181 (21.9%)	212 (30.0%)	90 (25.1%)
Any neuropsychiatric history	180 (9.5%)	74 (9.0%)	62 (8.8%)	44 (12.3%)
History of suicide or selfharm	4 (0.2%)	4 (0.5%)	0 (0.0%)	0 (0.0%)
History of severe depression or bipolar disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of other depression	140 (7.4%)	57 (6.9%)	50 (7.1%)	33 (9.2%)
History of other mood disorder	31 (1.6%)	12 (1.5%)	13 (1.8%)	6 (1.7%)
History of other mood disorder: anxiety alone (F41)	22 (1.2%)	10 (1.2%)	7 (1.0%)	5 (1.4%)
History of other mood disorder (not F41)	10 (0.5%)	3 (0.4%)	6 (0.8%)	1 (0.3%)
Schizophrenia-related disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
History of psychoanaleptics (EphMRA ATC codes N06a and N06C) [4]	27 (1.4%)	7 (0.8%)	10 (1.4%)	10 (2.8%)
History of minor tranquilizer (EphMRA ATC code N05 C)	3 (0.2%)	2 (0.2%)	0 (0.0%)	1 (0.3%)
History of antipsychotics (EphMRA ATC code N05A)	3 (0.2%)	2 (0.2%)	1 (0.1%)	0 (0.0%)
Prior NSAID treatment	956 (50.6%)	435 (52.7%)	343 (48.5%)	178 (49.6%)
Prior steroid treatment [5]	1605 (84.9%)	724 (87.8%)	583 (82.5%)	298 (83.0%)
Prior sulfasalazine treatment [6]	319 (16.9%)	162 (19.6%)	112 (15.8%)	45 (12.5%)
Prior methotrexate treatment	1330 (70.3%)	589 (71.4%)	500 (70.7%)	241 (67.1%)
Prior azathioprine treatment [7]	76 (4.0%)	52 (6.3%)	18 (2.5%)	6 (1.7%)
Prior leflunomide treatment	717 (37.9%)	311 (37.7%)	275 (38.9%)	131 (36.5%)
Prior hydroxychloroquine treatment	199 (10.5%)	91 (11.0%)	79 (11.2%)	29 (8.1%)
Prior **TNF-α** blocker treatment [8]	915 (48.4%)	421 (51.0%)	288 (40.7%)	206 (57.4%)

Comparisons that result in p values <0.05 are shown in bold. P values have not been corrected for multiple comparisons.

[1] P value for one-way Anova <0.0001. Mean follow-up time was significantly different in all three groups.
[2] P value for one-way Anova 0.0002. Mean age was significantly higher in the baricitinib group compared to the tofacitinib group and the tocilizumab group. There was no significant difference in mean age between tofacitinib and tocilizumab.
[3] P value for age group by treatment group interaction 0.0035 (Fisher's exact test).
[4] P value for history of psychoanaleptic treatment by treatment group interaction 0.0393 (Fisher's exact test).
[5] P value for history of systemic corticosteroid treatment by treatment group interaction 0.0078 (Fisher's exact test).
[6] P value for history of sulfasalazine treatment by treatment group interaction 0.0073 (Fisher's exact test).
[7] P value for history of azathioprine treatment by treatment group interaction <0.0001 (Fisher's exact test).
[8] P value for history of TNF-α blocker treatment by treatment group interaction <0.0001 (Fisher's exact test).

Table S 2 Incidence rates of neuropsychiatric events per 1000 person-years during the follow-up period

Incidence rate per 1000 P-Y (95% CI)						
	Patients without prior neuropsychiatric history (n=1711)			Patients with prior neuropsychiatric history (n=180)		
Event	Tofacitinib (n=751)	Baricitinib (n=645)	Tocilizumab (n=315)	Tofacitinib (n=74)	Baricitinib (n=62)	Tocilizumab (n=44)
Any neuropsychiatric outcome event	16.9 (9.2-28.3) (n=14)	21.1 (12.5-33.4) (n=18)	16.4 (7.1-32.4) (n=8)	129 (64.3-231) (n=11)	131 (56.4-258) (n=8)	206 (110-353) (n=13)
Suicide or selfharm	0.0 (0.0-4.5) (n=0)	0.0 (0.0-4.3) (n=0)	0.0 (0.0-7.6) (n=0)	0.0 (0.0-43.2) (n=0)	0.0 (0.0-60.3) (n=0)	0.0 (0.0-67.2) (n=0)
Severe depression or bipolar	0.0 (0.0-4.5) (n=0)	0.0 (0.0-4.3) (n=0)	0.0 (0.0-7.6) (n=0)	11.7 (0.3-65.3) (n=1)	0.0 (0.0-60.3) (n=0)	0.0 (0.0-67.2) (n=0)
Other depression	10.9 (5.0-20.6) (n=9)	7.0 (2.6-15.3) (n=6)	6.2 (1.3-18.0) (n=3)	93.7 (40.5-185) (n=8)	98.0 (36.0-213) (n=6)	206 (110-353) (n=13)
Other mood disorder	1.2 (0.0-6.7) (n=1)	3.5 (0.7-10.3) (n=3)	2.1 (0.1-11.4) (n=1)	35.1 (7.2-103) (n=3)	32.7 (4.0-118) (n=2)	0.0 (0.0-67.2) (n=0)
Anxiety (F41)	0.0 (0.0-4.5) (n=0)	1.2 (0.0-6.5) (n=1)	2.1 (0.1-11.4) (n=1)	35.1 (7.2-103) (n=3)	32.7 (4.0-118) (n=2)	0.0 (0.0-67.2) (n=0)
Other mood disorder (not F41)	1.2 (0.0-6.7) (n=1)	2.3 (0.3-8.5) (n=2)	0.0 (0.0-7.6) (n=0)	0.0 (0.0-43.2) (n=0)	0.0 (0.0-60.3) (n=0)	0.0 (0.0-67.2) (n=0)
Schizophrenia related	0.0 (0.0-4.5) (n=0)	1.2 (0.0-6.5) (n=1)	0.0 (0.0-7.6) (n=0)	0.0 (0.0-43.2) (n=0)	0.0 (0.0-60.3) (n=0)	0.0 (0.0-67.2) (n=0)
Treatment with N06A or N06C	7.2 (2.7-15.8) (n=6)	12.9 (6.4-23.1) (n=11)	10.3 (3.3-24.0) (n=5)	11.7 (0.3-65.3) (n=1)	65.4 (17.8-167) (n=4)	0.0 (0.0-67.2) (n=0)
Treatment with N05C	2.4 (0.3-8.7) (n=2)	0.0 (0.0-4.3) (n=0)	2.1 (0.1-11.4) (n=1)	0.0 (0.0-43.2) (n=0)	0.0 (0.0-60.3) (n=0)	0.0 (0.0-67.2) (n=0)
Treatment with N05A	1.2 (0.0-6.7) (n=1)	2.3 (0.3-8.5) (n=2)	0.0 (0.0-7.6) (n=0)	0.0 (0.0-43.2) (n=0)	0.0 (0.0-60.3) (n=0)	0.0 (0.0-67.2) (n=0)

Table S 3 Comparison between patients that did and patients that did not experience neuropsychiatric outcome events

	Patients with neuropsychiatric outcome event (n=72)	Patients without neuropsychiatric outcome event (n=1819)
Female patients	59 (81.9%)	1366 (75.1%)
Male patients	13 (18.1%)	453 (24.9%)
Mean number of days between first and last prescription (SD)	465.6 (257.9)	407.6 (279.4)
Median number of days between first and last prescription (IQR)	421 (289-554)	367 (196-544)
Mean age in years (SD) [1]	57.1 (12.0)	60.5 (13.5)
Median age in years (IQR)	57 (49-64)	61 (53-70)
Age 18-49 years [2]	19 (26.4%)	318 (17.5%)
Age 50-69 years	43 (59.7%)	1028 (56.5%)
Age **≥70** years	10 (13.9%)	473 (26.0%)
Prior NSAID treatment	29 (40.3%)	927 (51.0%)
Prior steroid treatment	56 (77.8%)	1549 (85.2%)
Prior sulfasalazine treatment [3]	3 (4.2%)	316 (17.4%)
Prior methotrexate treatment	50 (69.4%)	1280 (70.4%)
Prior azathioprine treatment	2 (2.8%)	74 (4.1%)
Prior leflunomide treatment	26 (36.1%)	691 (38.0%)
Prior hydroxychloroquine treatment	12 (16.7%)	187 (10.3%)
Prior **TNF-α** blocker treatment [4]	26 (36.1%)	889 (48.9%)
Concomitant NSAID treatment	24 (33.3%)	520 (28.6%)
Concomitant steroid treatment	50 (69.4%)	1175 (64.6%)
Concomitant sulfasalazine treatment	2 (2.8%)	29 (1.6%)
Concomitant methotrexate treatment	33 (45.8%)	677 (37.2%)
Concomitant azathioprine treatment	0 (0.0%)	10 (0.5%)
Concomitant leflunomide treatment	3 (4.2%)	58 (3.2%)
Concomitant hydroxychloroquine treatment	2 (2.8%)	26 (1.4%)
Concomitant TNF-α blocker treatment	10 (13.9%)	221 (12.1%)

Comparisons that result in p values <0.05 are shown in bold. P values have not been corrected for multiple comparisons.

[1] P value for the difference in mean age 0.0335 (T-test, pooled method, equal variance).

[2] P value for age group by outcome interaction 0.023 (Fisher's exact test).

[3] P value for history of treatment with sulfasalazine by outcome interaction 0.0019 (Fisher's exact test).

[3] P value for history of treatment with TNF-α blockers by outcome interaction 0.0404 (Fisher's exact test).

Table S 4 Comparison between patients that did and patients that did not experience neuropsychiatric outcome events limited to patients with no neuropsychiatric history

	Patients with neuropsychiatric outcome event (n=40)	Patients without neuropsychiatric outcome event (n=1671)
Female patients	30 (75.0%)	1237 (74.0%)
Male patients	10 (25.0%)	434 (26.0%)
Mean number of days between first and last prescription (SD)	470.0 (262.5)	408.2 (279.0)
Median number of days between first and last prescription (IQR)	436.5 (249.5-577)	373 (196-544)
Mean age in years (SD)	56.8 (12.6)	60.5 (13.6)
Median age in years (IQR)	55.5 (49.5-64.5)	61 (53-70)
Age 18-49 years	10 (25.0%)	297 (17.8%)
Age 50-69 years	23 (57.5%)	930 (55.7%)
Age ≥70 years	7 (17.5%)	444 (26.6%)
Prior NSAID treatment [1]	12 (30.0%)	837 (50.1%)
Prior steroid treatment	31 (77.5%)	1419 (84.9%)
Prior sulfasalazine treatment	2 (5.0%)	288 (17.2%)
Prior methotrexate treatment	27 (67.5%)	1166 (69.8%)
Prior azathioprine treatment	2 (5.0%)	69 (4.1%)
Prior leflunomide treatment	13 (32.5%)	622 (37.2%)
Prior hydroxychloroquine treatment	6 (15.0%)	166 (9.9%)
Prior TNF-α blocker treatment	18 (45.0%)	820 (49.1%)
Concomitant NSAID treatment	8 (20.0%)	467 (27.9%)
Concomitant steroid treatment	27 (67.5%)	1078 (64.5%)
Concomitant sulfasalazine treatment	2 (5.0%)	26 (1.6%)
Concomitant methotrexate treatment	17 (42.5%)	625 (37.4%)
Concomitant azathioprine treatment	0 (0.0%)	9 (0.5%)
Concomitant leflunomide treatment	1 (2.5%)	54 (3.2%)
Concomitant hydroxychloroquine treatment	1 (2.5%)	20 (1.2%)
Concomitant TNF-α blocker treatment	6 (15.0%)	202 (12.1%)

Comparisons that result in p values <0.05 are shown in bold. P values have not been corrected for multiple comparisons.

[1] P value for history of treatment with NSAIDs by outcome interaction 0.0155 (Fisher's exact test).

Annex 4 Feasibility Feedback

Feasibility Analysis

Patients with a minimum of 365 days of observation prior to the first initiation of a JAK inhibitor were included in the feasibility analysis. Patient were followed until the end of follow-up for the patient, which is the last consultation date for the patient, and did not take into account when treatment was discontinued (i.e. ever exposed patients included in feasibility assessment).

The feasibility analysis has not been performed by practice speciality (e.g. by GPs, internal medicine specialist, etc.).

Recording of the following events was analysed:

- Mania/bipolar or severe depression: ICD 10 codes F30 (manic episode), F31 (bipolar affective disorder), F32.3 (severe depressive episode with psychotic symptoms) and F33.3 (recurrent depressive disorder, current episode severe with psychotic symptoms)
- Other depression: ICD 10 codes F32.0-F32.2, F32.8-F32.9 (depressive episode), F33.0-F33.2, F33.8-F33.9 (recurrent depressive disorder)
- Other mood disorder: ICD 10 codes F34 (persistent mood disorders), F38 (other mood disorders), F39 (unspecified mood disorder), F41 (Other anxiety disorders), F42 (Obsessive-compulsive disorder), F43 (Reaction to severe stress, and adjustment disorders), F60.3 (emotionally unstable personality disorder), R45.0-R45.7 (symptoms and signs involving emotional state)
- Schizophrenia-related disorder: ICD 10 codes F20 to F29 (schizophrenia, schizotypal and delusional disorders), R44.0 (Auditory hallucinations), R44.1 (Visual hallucinations), R44.2 (Other hallucinations), R44.3 (Hallucinations, unspecified), R44.8 (Other and unspecified symptoms and signs involving general sensations and perceptions)
- Suicidal and self-harm events: ICD 10 codes Z91.5 (personal history of self-harm), R45.8 (Other symptoms and signs involving emotional state such as suicidal ideation (tendencies)), and ICD codes Z91.8 (personal history of other specified risk-factors, not elsewhere classified), T14.9 (injury unspecified), Z72.8 (unspecified problem related to lifestyle) where associated with a medical event text indicating a suicidal or self-harm event

Over the whole observation time in the database (updated June 2020), a total of 2223 patients started treatment with a JAK inhibitor and had at least 365 days of observation. Of these, 283 patients had a history of any of the above neuropsychiatric events, and 1940 patients had no such history. A total of 87 patients experienced a neuropsychiatric event during follow-up of which 51 patients had neuropsychiatric history and 36 patients had no neuropsychiatric history. There was no suicidal or self-harm event reported during the follow-up period (and only one patient each had an event of severe depression/bipolar and schizophrenia related event.

Events regarding anxiety are included in ‘other mood disorders’ and which were as a group of events recorded in a low number of patients receiving tofacitinib (overall 15, thereof 8 with history of mood disorders and 7 without).

Please see below for a breakdown of neuropsychiatric history and neuropsychiatric events for the different JAK inhibitors.

Feasibility counts for JAK inhibitors

Patients with at least 365 days of observation prior to initiation of treatment

SUBSTANCE	Total no of patients	No of patients with neuropsychiatric history	No of patients with no neuropsychiatric history
BARICITINIB	962	122	840
RUXOLITINIB	76	18	58
TOFACITINIB	1096	132	964
UPADACITINIB	89	11	78

Neuropsychiatric event any time after initiation of treatment

SUBSTANCE	Total no of patients with	No of patients with neuropsychiatric history	No of patients with no neuropsychiatric history
BARICITINIB	35	24	11
RUXOLITINIB	10	3	7
TOFACITINIB	42	24	18
UPADACITINIB	0	0	0

Severe depression/bipolar event any time after initiation of treatment

SUBSTANCE	Total no of patients	No of patients with neuropsychiatric history	No of patients with no neuropsychiatric history
BARICITINIB	0	0	0
RUXOLITINIB	0	0	0
TOFACITINIB	1	1	0
UPADACITINIB	0	0	0

Other depression event any time after initiation of treatment

SUBSTANCE	Total no of patients	No of patients with neuropsychiatric history	No of patients with no neuropsychiatric history
BARICITINIB	26	19	7
RUXOLITINIB	3	1	2
TOFACITINIB	35	21	14
UPADACITINIB	0	0	0

Other mood event any time after initiation of treatment

SUBSTANCE	Total no of patients	No of patients with neuropsychiatric history	No of patients with no neuropsychiatric history
BARICITINIB	14	11	3
RUXOLITINIB	7	2	5
TOFACITINIB	15	8	7
UPADACITINIB	0	0	0

Schizophrenia related any time after

SUBSTANCE	Total no of patients	No of patients with neuropsychiatric history	No of patients with no neuropsychiatric history
BARICITINIB	1	0	1
RUXOLITINIB	0	0	0
TOFACITINIB	0	0	0
UPADACITINIB	0	0	0

Feasibility counts for TNF alfa blockers and tocilizumab

The number of patients receiving TNF alfa blockers and tocilizumab is provided in the table below by practice speciality.

Practice speciality	Adali-mumab	Certoli-zumab	Etan-ercept	Goli-mumab	Inflixi-mab	Tocili-zumab
Dermatology	1335	60	475	25	81	4
Gynecology	46	7	16	2	14	3
Internal Medicine & General Practice with Focus	7029	1705	6004	1440	1739	1507
GPs	974	118	825	134	131	129
Neurology	4	2	2	2	0	3
Orthopedics	166	31	245	15	22	39
Otolaryngology	31	9	28	5	13	4
Pediatrics	137	2	205	7	6	19
Psychiatry	2	0	0	1	0	0
Urology	24	2	18	1	11	4

Recommended Data Source

IMS® Disease Analyzer Germany (TBD)

Proposed timelines for analysis

Feasibility feedback with analysis proposal shared with Rapporteur	24 September 2020
Feedback from Rapporteur on proposed analysis	2 October 2020
Draft analysis protocol circulated to Rapporteur and PRAC Members for comments	TBD *(proposal in case of further analyses: 9 October 2020)*
Comments from Rapporteur and PRAC Members on draft analysis plan by	TBD *(proposal in case of further analyses: 16 October 2020)*
Updated analysis plan following comments circulated by EMA to Rapporteurs and PRAC Members by	TBD *(proposal in case of further analyses: 20 October 2020)*
Analysis report by EMA circulated to Rapporteurs and PRAC Members by	TBD

Proposed analysis by data analyst (brief outline as basis for development of analysis plan)

The number of psychiatric events recorded ever after treatment initiation with JAK inhibitors is rather low. Most of the recorded events are events of 'other depression'. Other mood disorders are also recorded, but at lower rate. Considering that these events include all events after treatment initiation, the number of events during treatment, e.g. defined by a certain exposure time window after treatment initiation, will likely be lower. Furthermore, events of depression are difficult to interpret due to confounding by underlying indication in patients with rheumatoid arthritis. Comparative analyses comparing incidence rates of JAK inhibitors to other classes might be envisaged but will still depend on low event rates and therefore will result in estimates with high variability.

Regarding the recorded events of other mood disorders, including anxiety, it is also noted that the event number is low and that this relates to ever recorded events. An even lower number of events is expected if events are restricted to a certain time window after exposure.

Therefore, if an analysis is performed, we would propose to perform descriptive analyses describing patient demographics (including indication for treatment if available), time to event recordings and to derive incidence rates for patients with and without history of psychiatric events in JAK inhibitors, if considered helpful. A comparative analysis is not proposed at this stage due to anticipated low event counts and uncertain effect estimates.