EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 October 2019
EMA/631064/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Xeljanz

INN/active substance: tofacitinib

Procedure number: EMEA/H/A-20/1485/C/4214/0017

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

On 15 May 2019 the European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of a potential increased risk of pulmonary embolism (PE) and overall mortality on the benefit-risk balance of Xeljanz and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Study A3921133 is an on-going open labelled clinical study that evaluates the safety of tofacitinib 5 mg twice daily (BID) and tofacitinib 10 mg BID compared to a tumour necrosis factor inhibitor (etanercept or adalimumab) in patients with rheumatoid arthritis (RA). The study is a post-authorisation commitment intended to assess the risk of cardiovascular events with tofacitinib in patients 50 years of age or older who have at least one additional cardiovascular risk factor, e.g. current smoker, high blood pressure, high cholesterol levels, diabetes mellitus, history of heart attack, family history of coronary heart disease, extra-articular RA disease. All patients entered the study on stable doses of background methotrexate.

On 12 February 2019 the marketing authorisation holder (MAH) informed the European Medicines Agency (EMA) that an increased risk of pulmonary embolism (PE) and overall mortality had been reported in Study A3921133. In this clinical trial, the overall incidence of PE was 5.96-fold higher in tofacitinib 10 mg twice daily arm of the study compared with the TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib development programme. The data safety monitoring board (DSMB) recommended to modify Study A3921133 to discontinue treatment with tofacitinib 10 mg BID. Of note, the FDA subjected the continuation of the trial to the condition that subjects assigned to the 10 mg BID dose were switched to the lower 5 mg BID dose.

Following to the information received from the MAH, a direct healthcare professional communication (DHPC) was circulated in EU Member States at the end of March 2019 to inform prescribers about the data emerging from study A3921133. Further, the EMA started to assess the increased risk of PE and overall mortality in patients treated with tofacitinib 10 mg twice daily and its potential impact on the marketing authorisation for Xeljanz in a signal procedure. Based on the information available and assessed during the signal procedure, PRAC concluded that tofacitinib is associated with a dose dependent risk of PE.

In view of the seriousness of PE and uncertainties about the underlying mechanism, the PRAC decided that the impact of these findings on the benefit-risk balance of tofacitinib in all authorised indications and doses should be fully assessed resulting in a referral notification. In view of the seriousness of the risk, PRAC recommended the introduction of provisional measures while the review was ongoing. A second DHPC has been circulated at the end of May 2019 to inform prescribers about these provisional measures.

Xeljanz contains tofacitinib which is a selective inhibitor of the Janus kinase (JAK) family of kinases. Tofacitinib is a JAK 1, 2 and 3 inhibitor and is classified as an oral disease modifying anti-rheumatic drug (DMARD). Inhibition of JAK1 and JAK3 attenuates signalling of interleukins (IL2, 4, 7, 9, 15 and 21) and interferons type I/II, resulting in modulation of the immune and inflammatory response.

In the EU, Xeljanz was granted a marketing authorisation on 21 March 2017, for the treatment of rheumatoid arthritis (RA). In June 2018, it was approved for treatment of psoriatic arthritis (PsA), and in July 2018, it was also approved for the treatment of ulcerative colitis (UC).

In the EU, tofacitinib is authorised as a 5 and 10 mg film coated tablet. The recommended dose for RA and PsA is 5 mg twice daily, and for UC, the recommended dose is 10 mg twice a day for the first 8 weeks and thereafter 5 mg twice a day. For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. For some patients, such as those who have failed prior tumour necrosis factor (TNF) antagonist therapy, consideration should be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit. Patients who experience a decrease in response on tofacitinib 5 mg twice daily maintenance therapy may benefit from an increase to tofacitinib 10 mg administered twice daily.

2.2. Non-clinical aspects

The MAH was requested to provide a potential mechanistic explanation for the increased rate of pulmonary embolism (PE) in patients from Study A3921133 with additional risk factors.

Several potential mechanisms were discussed by the MAH such as a potential relationship between tofacitinib and clotting-related factors – including tissue factor; a potential role for pro-inflammatory cytokines such as TNF and IL-6 and the complex interaction between monocytes, neutrophils, platelets, and the coagulation cascade; and numerous pro- and anti-coagulant factors that regulate the clotting cascade, but for which the role of JAK-STAT signalling in the regulation of these various pathways, either directly or indirectly, is not well characterized. It is however not clear which mechanisms play a predominant role.

Although standard toxicology studies did not provide a clear signal of a prothrombogenic effect of tofacitinib, these studies were considered to have limitations with respect to the frequency of measurement of coagulation parameters and platelet counts and as such results need to be interpreted with caution.

The MAH was also requested to discuss a rebound effect on platelet formation as a potential mechanism and provide the available non-clinical and clinical data that would support or contradict this mechanism. The MAH acknowledged that clinical pathology parameters in animal toxicity studies are not typically frequent enough to identify transient changes in such parameters, therefore although sustained changes in platelets were not observed, an absence of transient effects on platelets, either during dosing or recovery phases of animal toxicity studies cannot definitively be concluded on. Moreover, thrombopoietin (TPO) levels were not evaluated in the non-clinical studies. Consequently, for additional parameters and evaluation of temporary changes in platelet counts the only available evidence comes from clinical data. Routine monitoring of platelet counts in clinical studies revealed that in the first week after starting treatment, the platelet counts slightly increased, followed by a decrease from baseline (nadir at Week 4). There was no signal of rebound after stopping tofacitinib. When looking at the platelet counts in PE cases, no clear pattern could be distinguished as most patients had platelet counts within the normal range when the event occurred. Altogether, the totality of the data do not indicate that routine monitoring of platelets in clinical practice would be of use to prevent VTE/PE in patients treated with tofacitinib and therefore no specific recommendations have been introduced in the product information.

The role of inflammatory response in the development of VTE, as described by Branchford et al. 2018[1], was also discussed as a potential mechanism. Inflammation of the vessel wall initiates thrombus formation in an intact vein and that inflammation and coagulation systems are coupled by a common activation pathway.

The MAH was also requested to conduct analysis to study possible association between infections and VTE events (e.g. within 3 months period preceding the VTE events, i.e. PE or DVT) based on pooled tofacitinib studies. While an increased risk of serious infections has been observed for tofacitinib versus active comparator TNF-inhibitors in Study A3921133, due to low number of VTE events, it was difficult to establish to what extent infections have contributed to the risk of VTE.

Although the exact mechanism is not yet clear, PRAC concluded that a potential role of JAK2 inhibition by tofacitinib in relation with the increased incidence of PE in patients treated with tofacitinib cannot be excluded.

The MAH has initiated further research aiming at identifying potential biomarkers by analysis of samples from study A3921133, encompassing Factor V Leiden rs6025 Genotyping, Prothrombin rs1799963 Genotyping, JAK2 rs12343867 Genotyping, D-dimer, Apolipoprotein-CIII, Leptin, Thrombopoietin, Plasminogen Activator Inhibitor 1, Anti-thrombin III ELISA, Tissue Factor Pathway Inhibitor, Thrombin/anti-thrombin complexes, Factor VIII Antigen ELISA, Protein C ELISA, Olink Proteomic Panels and Anti-phospholipid antibody (anticardiolipin abs, beta-2-glycoprotein) IgG, IgM. For those biomarkers that distinguished tofacitinib from placebo-control, a comparison to an active control DMARD (other than a JAK inhibitor, e.g. TNFi) would be of interest to further contextualise the effects –which may be either treatment-related, or due to altered disease state.

The ongoing VTE biomarker study has been included as a category 3 study in the RMP. The MAH is requested to consider the inclusion of an active control (TNFi). The final report is expected for September 2020.

2.3. Data on efficacy

The efficacy of Xeljanz in its authorised indications has been previously established and is not questioned in the present procedure.

2.4. Data on safety

2.4.1. Thrombotic events

Study A3921133

Study A3921133 included patients with active moderate to severe rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX) and who were 50 years of age or older and had at least one cardiovascular risk factor (e.g. current smoker, high blood pressure, high cholesterol levels, diabetes mellitus, history of heart attack, family history of coronary heart disease, extra-articular RA disease). Background MTX was required for all enrolled patients. Patients in the active comparator arm were treated with TNF inhibitors (etanercept or adalimumab).

In February 2019, the rheumatology data safety monitoring board (DSMB) on tofacitinib reported that there is a statistically and clinically important difference in the occurrence of pulmonary embolism and increased mortality within the tofacitinib 10 mg BID treatment arm compared to the TNFi control arm.

[1] Branchford BR and Carpenter SL (2018). The Role of Inflammation in Venous Thromboembolism. Front. Pediatr. 6:142. doi: 10.3389/fped.2018.00142

Available interim analyses to review the increased risk of thrombotic events and overall mortality in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily, and its potential impact on the marketing authorisation for tofacitinib in all indications are presented below.

The results of study A3921133 show that in RA patients aged ≥50 years and with at least one CV risk factor, there is an increased risk for developing PE and deep venous thrombosis (DVT) if treated with tofacitinib. This increase is dose dependent. Compared to treatment with a TNF inhibitor (adalimumab or etanercept), the risk for PE is about 6-fold higher in the 10 mg BID group and about 3-fold higher for the 5 mg BID group compared to the control group. For DVT, the risk was increased in tofacitinib 5 mg BID and 10 mg BID compared to TNF inhibitor treatment, although statistical significance was not reached. Considering the pathophysiology of these conditions (PE and DVT are both manifestations of venous thromboembolism), the signal for increased risk of DVT is considered relevant. Increase in risk for arterial thromboembolism (ATE) was not statistically significant (table 1).

Table 1 - Overall Rates for Pulmonary Embolism (PE), Deep Vein Thrombosis (DVT), Arterial Thromboembolism (ATE) and Mortality for Study A3921133 (28 Day IR Algorithm)

Tofacitinib **5 mg BID** **n/N** **PY** **IR (95% CI)**	**Tofacitinib** **10 mg BID** **n/N** **PY** **IR (95% CI)**	**TNFi** **n/N** **PY** **IR (95% CI)**
Pulmonary Embolism (PE)		
9/1458 3317.11 0.27 (0.12, 0.52)	17/1453 3122.77 0.54 (0.32, 0.87)	3/1451 3318.74 0.09 (0.02,0.26)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi	2.99 (0.81, 11.06)	
10 mg BID to TNFi	5.96 (1.75, 20.33)	
10 mg BID to 5 mg BID	2.01 (0.90, 4.52)	
Deep Vein Thrombosis (DVT)		
10/1458 3316.37 0.30 (0.14, 0.55)	12/1453 3132.18 0.38 (0.20, 0.67)	6/1451 3320.52 0.18 (0.07, 0.39)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi	1.66 (0.60, 4.57)	
10 mg BID to TNFi	2.13 (0.80, 5.69)	
10 mg BID to 5 mg BID	1.27 (0.55, 2.95)	
Arterial Thromboembolism (ATE)		
21/1458 3308.19 0.63 (0.39,0.97)	23/1453 3114.86 0.74 (0.47,1.11)	20/1451 3299.46 0.61 (0.37,0.94)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi	1.04 (0.57, 1.92)	
10 mg BID to TNFi	1.22 (0.67, 2.23)	
10 mg BID to 5 mg BID	1.18 (0.65, 2.12)	
Deaths - 28 Day IR Algorithm		
19/1458 3323.95 0.57 (0.34,0.89)	28/1453 3140.31 0.89 (0.59,1.29)	9/1451 3323.27 0.27 (0.12,0.51)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi	2.11 (0.96, 4.67)	
10 mg BID to TNFi	3.28 (1.55, 6.95)	
10 mg BID to 5 mg BID	1.55 (0.87, 2.78)	

Tofacitinib 5 mg BID n/N PY IR (95% CI)	Tofacitinib 10 mg BID n/N PY IR (95% CI)	 TNFi n/N PY IR (95% CI)

*Only events occurring within 28 days after the last dose or to the data-lock point are included in this table. PY is calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or death date or to the data-lock point. HR and its associated CI were estimated from a Cox regression model including fixed effects of treatment (only the treatment groups involved for the comparison). Data-lock point: 22FEB2019. Abbreviations: BID = twice daily; CI = confidence interval; CV = cardiovascular risk factor; HDL = high density lipoprotein; HR = hazard ratio; IR = incidence rate; LTE = long-term extension; n = number of patients with events; N= total number of patients; PY = patient-years; RA = rheumatoid arthritis, TNFi = tumour necrosis factor inhibitor.

Data from non A3921133 studies

The MAH provided analyses of PE, DVT, ATE, MACE, and mortality in tofacitinib treated patients, 5 mg BID and 10 mg BID, compared with the active comparator arm or placebo using pooled clinical trial data per indication. The comparative analyses were organized as:

1) Cohort 1: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Psoriasis (PsO) and Ulcerative Colitis (UC) in (placebo-control period 0-3 months), RA, PsA, PsO and UC Cohort 2 (full randomized period 0-24 months) and RA, PsA, PsO and UC, Cohort 3 datasets ('all tofacitinib including long term data'), without RA study 1133 (*pooled registration trial data*).
2) The RA dataset from Cohort 3 was used to compare CVD 'enriched' versus 'non-enriched' subgroups of pooled RA pre-registration trials.

1) Pooled registration trial data

The results of pooled clinical trial data sets in RA (non-1133), PsA, PsO and UC patients show lower occurrence of events, notably PE and DVT, compared to study 1133, and no clear signal for thrombotic events had emerged from these trials.

For the largest study population from pre-registration clinical trials, i.e. pooled data of RA patients, few cases of PE were reported for tofacitinib in the controlled study phases of the pre-registration clinical trials, in a dose-dependent way, versus none in the active control groups (table 2). For DVT, also only a few cases were reported, though with an inverse dose relationship, and lower incidence than active controls or placebo (table 3).

For UC, neither cases of PE nor of DVT were reported in the controlled study phase, but only in the extension phase (tofacitinib exposure 217 to 1149 days), and for the highest (10 mg BID) dose (n/N = 4/960; IR (95% CI) 0.21 (0.06, 0.55)). Altogether, although the cases were rare, there is a slight tendency of dose-dependency for PE in the UC trials.

Table 2 - Overall Incidence Rates and Hazard Ratios/Incidence Rate Differences for Pulmonary Embolism (PE) for Tofacitinib Clinical Program (28-Day IR Algorithm)*

Placebo Control 0-3 Months† n/N PY IR (95% CI)	Full Randomized Period 0-24 Months† n/N PY IR (95% CI)	All Tofacitinib (average daily dose)† n/N PY IR (95% CI)	All Tofacitinib† n/N PY IR (95% CI)

Rheumatoid Arthritis (RA) ‡								
Tofacitinib 5 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**Combined Doses**
0/1849 449.43 0.00 (0.00,0.82)	1/1079 242.63 0.4 (0.01, 2.30)	0/22354.48 0.00 (0.00, 6.77)	0/25762.09 0.00 (0.00, 5.94)	2/1849 1867.01 0.11 (0.01, 0.39)	0/223 301.42 0.00 (0.00, 1.22)	0/257 196.42 0.00 (0.00, 1.88)	8/30668395.39 0.10 (0.04, 0.19)	28/706123416.62 0.12 (0.08, 0.17)
Tofacitinib 10 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 10 mg**	**MTX**	**ADA**	**Tofacitinib 10 mg**	
0/2024 484.07 0.00 (0.00,0.76)	NA	NA	NA	3/2024 1998.07 0.15 (0.03, 0.44)	NA	NA	20/399515021.23 0.13 (0.08, 0.21)	
Pair-Wise Comparisons (RA)		**HR (95% CI)**		**Pair-Wise Comparisons (RA)**		**HR (95% CI)**	NA	
Tofacitinib 5 mg BID to Placebo Tofacitinib 10 mg BID to Placebo Tofacitinib 10 mg BID to 5 mg BID		NE NE NE		Tofacitinib 10 mg BID to 5 mg BID		1.36 (0.22, 8.30)		
Ulcerative Colitis (UC) ∞								
Tofacitinib 5 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**Combined Doses**
NA	1/28250.46 1.98 (0.05, 11.04)	NA	NA	0/198 148.77 0.00 (0.00, 2.48)	NA	NA	0/197 606.49 0.00 (0.00, 0.61)	4/11572468.64 0.16 (0.04, 0.41)
Tofacitinib 10 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 10 mg**	**MTX**	**ADA**	**Tofacitinib 10 mg**	
0/938 166.08 0.00 (0.00, 2.22)	NA	NA	NA	0/196 157.31 0.00 (0.00, 2.35)	NA	NA	4/960§ 1862.15 0.21 (0.06, 0.55)	
Pair-Wise Comparisons (UC)		**IR diff (95% CI)**		**Pair-Wise Comparisons (UC)**		**IR diff (95% CI)**	NA	
Tofacitinib 10 mg BID to Placebo		-1.98 (-5.87, 1.90)		Tofacitinib 5 mg BID to Placebo Tofacitinib 10 mg BID to Placebo Tofacitinib 10 mg BID to 5 mg BID		-0.98 (-2.89, 0.94) -0.98 (-2.89, 0.94) 0.00 (0.00, 0.00)		

*Only events occurring within 28 days after the last dose are included in this table. PY was counted to the time to the first event for subjects with events or up to the last dose plus 28 days for subjects without events.
†Each column results include number of patients with events, total number of patients within each treatment arm, incidence rate, and 95% CI unless otherwise specified.
‡RA Programme: Full randomized period consisted of pooled data from Phase 2 studies and Phase 3 studies ranging from 0 up to 6 to 24 months duration; All tofa data data-lock point 02 Mar 2017.
±PsO Programme: Full randomized period consisted of pooled data from Phase 3 studies of 0-12 months duration; All tofa final data 18 Aug 2016.
¶ PsA Programme: Full randomized period consisted of pooled data from Phase 3 studies ranging from 0 up to 6 to 12 months duration All tofa data data-lock point 31 Aug 2017.

∞UC Programme: Pooled data from 1 Phase 2 and 2 Phase 3 induction studies of 8 weeks duration, which included placebo and 10 mg BID dose but did not include 5 mg BID dose; full randomized period consisted of 1 Phase 3 maintenance study of 12 months duration (following participation in an induction study, all patients were re-randomized at the baseline of the maintenance study); All tofa data data-lock point 21 Sep 2018.
§As shown, the incidence rate for the average daily 10 mg BID arm is higher than the rate for average daily 5 mg BID. Of note, the exposure to 10 mg BID dose was approximately 3-fold higher than the exposure to the 5 mg BID dose.
Abbreviations: ADA = Adalimumab; BID = twice daily; CI = confidence interval; diff = difference; HR = hazard ratio; IR = incidence rate; MTX = Methotrexate; n = number of patients with events; N= total number of patients in treatment arm; NA = Not Applicable; NE = not estimable due to 0 event in at least one treatment group in a comparison; PE = pulmonary embolism; PsA = psoriatic arthritis; PsO = psoriasis; PY = Patient-Years; RA = rheumatoid arthritis; tofa = tofacitinib; UC = ulcerative colitis.

Table 3 - Overall Incidence Rates and Hazard Ratios/Incidence Rate Differences for Deep Vein Thrombosis (DVT) for Tofacitinib Clinical Program (28-Day IR Algorithm)*

Placebo Control 0-3 Months† **n/N** **PY** **IR** **(95% CI)**				**Full Randomized Period 0-24 Months†** **n/N** **PY** **IR** **(95% CI)**			**All Tofacitinib (average daily dose)†** **n/N** **PY** **IR** **(95% CI)**	**All Tofacitinib†** **n/N** **PY** **IR** **(95% CI)**
Rheumatoid Arthritis (RA) ‡								
Tofacitinib 5 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**Combined Doses**
0/1849 449.43 0.00 (0.00, 0.82)	1/1079 242.63 0.41 (0.01, 2.30)	1/223 54.30 1.84 (0.05, 10.26)	0/257 62.09 0.00 (0.00, 5.94)	3/1849 1865.44 0.16 (0.03, 0.47)	1/223 300.33 0.33 (0.01, 1.86)	0/257 196.42 0.00 (0.00, 1.88)	13/3066 8380.54 0.16 (0.08, 0.27)	36/7061 23391.24 0.15 (0.11, 0.21)
Tofacitinib 10 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 10 mg**	**MTX**	**ADA**	**Tofacitinib 10 mg**	
1/2024 484.07 0.21 (0.01, 1.15)	NA	NA	NA	2/2024 1998.34 0.10 (0.01, 0.36)	NA	NA	23/3995 15010.70 0.15 (0.10, 0.23)	
Pair-Wise Comparisons (RA)		**HR (95% CI)**		**Pair-Wise Comparisons (RA)**		**HR (95% CI)**	NA	
Tofacitinib 5 mg BID to Placebo		NE		Tofacitinib 10 mg BID to 5 mg BID		0.62 (0.10, 3.74)		
Tofacitinib 10 mg BID to Placebo		0.39 (0.02, 6.39)						
Tofacitinib 10 mg BID to 5 mg BID		NE						

Placebo Control 0-3 Months† n/N PY IR (95% CI)				Full Randomized Period 0-24 Months† n/N PY IR (95% CI)			All Tofacitinib (average daily dose)† n/N PY IR (95% CI)	All Tofacitinib† n/N PY IR (95% CI)
Ulcerative Colitis (UC) ∞								
Tofacitinib 5 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**MTX**	**ADA**	**Tofacitinib 5 mg**	**Combined Doses**
NA	1/282 50.31 1.99 (0.05, 11.07)	NA	NA	0/198 148.77 0.00 (0.00, 2.48)	NA	NA	0/197 606.49 0.00 (0.00, 0.61)	1/1157 2472.63 0.04 (0.00, 0.23)
Tofacitinib 10 mg	**Placebo**	**MTX**	**ADA**	**Tofacitinib 10 mg**	**MTX**	**ADA**	**Tofacitinib 10 mg**	
0/938 166.08 0.00 (0.00, 2.22)	NA	NA	NA	0/196 157.31 0.00 (0.00, 2.35)	NA	NA	1/960 1866.14 0.05 (0.00, 0.30)	
Pair-Wise Comparisons (UC)		**IR diff (95% CI)**		**Pair-Wise Comparisons (UC)**		**IR diff (95% CI)**	NA	
Tofacitinib 10 mg BID to Placebo		-1.99 (-5.88, 1.91)		Tofacitinib 5 mg BID to Placebo Tofacitinib 10 mg BID to Placebo Tofacitinib 10 mg BID to 5 mg BID		-0.97 (-2.86, 0.93) -0.97 (-2.86, 0.93) 0.00 (0.00, 0.00)		

*Only events occurring within 28 days after the last dose are included in this table. PY was counted to the time to the first event for subjects with events or up to the last dose plus 28 days for subjects without events.
†Each column results include number of patients with events, total number of patients within each treatment arm, incidence rate, and 95% CI unless otherwise specified.
‡RA Programme: Full randomized period consisted of pooled data from Phase 2 studies and Phase 3 studies ranging from 0 up to 6 to 24 months duration; All tofa data data-lock point 02 Mar 2017.
∞UC Programme: Pooled data from 1 Phase 2 and 2 Phase 3 induction studies of 8 weeks duration, which included placebo and 10 mg BID dose but did not include 5 mg BID dose; full randomized period consisted of 1 Phase 3 maintenance study of 12 months duration (following participation in an induction study, all patients were re-randomized at the baseline of the maintenance study); All tofa data data-lock point 21 Sep 2018.
§As shown, the incidence rate for the average daily 10 mg BID arm is higher than the rate for average daily 5 mg BID. Of note, the exposure to 10 mg BID dose was approximately 3-fold higher than the exposure to the 5 mg BID dose.
Abbreviations: ADA = Adalimumab; BID = twice daily; CI = confidence interval; diff = difference; DVT = deep vein thrombosis; HR = hazard ratio; IR = incidence rate; MTX = Methotrexate; n = number of patients with events; N= total number of patients in treatment arm; NA = Not Applicable; NE = not estimable due to 0 event in at least one treatment group in a comparison; PY = Patient-Years; RA = rheumatoid arthritis; tofa = tofacitinib; UC = ulcerative colitis.

Comparison of sub-groups 'enriched' versus 'non-enriched' with cardiovascular risk factors in non-1133 registration RA cohort 3

In these analyses there was a tendency for increased rates of MACE, Arterial Thromboembolism, DVT and PE for patients with one or more CV risk factors at baseline in these post-hoc analyses versus patients without CV risk factors at baseline (Table 4). Dose-dependency was less clear in these post-hoc analyses.

For the other indications (UC and PsA), post-hoc analyses in a CV enriched population could not be performed due to the limited number of events in non-RA studies.

Table 4 - Number of Subjects with Events and Incidence Rates for Pulmonary Embolism (PE), Deep Vein Thrombosis (DVT), Arterial Thromboembolism (ATE), and Major Adverse Cardiovascular Events (MACE) for Tofacitinib RA P123LTE by Baseline CV Risk Factor * (28-Day IR Algorithm)

Baseline CV Risk Factor	Tofacitinib Average Daily 5 mg BID n/N PY IR (95% CI)	Tofacitinib Average Daily 10 mg BID n/N PY IR (95% CI)	All Tofacitinib n/N PY IR (95% CI)
Pulmonary Embolism (PE)**			
Yes	6/1190 3227.98 0.19 (0.07, 0.40)	13/1512 5386.05 0.24 (0.13, 0.41)	19/2702 8614.03 0.22 (0.13, 0.34)
No	2/1876 5167.41 0.04 (0.00,0.14)	7/2483 9635.18 0.07 (0.03, 0.15)	9/4359 14802.59 0.06 (0.03, 0.12)
Deep Vein Thrombosis (DVT)**			
Yes	10/1190 3214.84 0.31 (0.15, 0.57)	9/1512 5390.57 0.17 (0.08, 0.32)	19/2702 8605.41 0.22 (0.13, 0.34)
No	3/1876 5165.69 0.06 (0.01, 0.17)	14/2483 9620.14 0.15 (0.08, 0.24)	17/4359 14785.83 0.11 (0.07, 0.18)
Arterial Thromboembolism (ATE)**			
Yes	22/1190 3207.94 0.69 (0.43, 1.04)	43/1512 5290.38 0.81 (0.59, 1.09)	65/2702 8498.32 0.76 (0.59, 0.97)
No	6/1876 5165.47 0.12 (0.04, 0.25)	13/2483 9603.43 0.14 (0.07, 0.23)	19/4359 14768.90 0.13 (0.08, 0.20)
Major Adverse Cardiovascular Events (MACE)**			
Yes	23/1097 2891.62 0.80 (0.50, 1.19)	35/1422 5247.35 0.67 (0.46, 0.93)	58/2519 8138.97 0.71 (0.54, 0.92)
No	8/1739 4696.41 0.17 (0.07, 0.34)	19/2359 9504.69 0.20 (0.12, 0.31)	27/4098 14201.10 0.19 (0.13, 0.28)

*Baseline Cardiovascular Risk = subject who was >=50 years AND has any of the following conditions at baseline: current smoker, HDL<40 mg/dL, hypertension, diabetes, myocardial infarction or coronary heart disease.
**Only events occurring within 28 days after the last dose are included in this table. PY is calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or to the data-lock point.
Exact Poisson (adjusted for PY) 95% confidence intervals are provided for the crude incidence rate.
Includes Protocols - A392- 1019, 1024, 1025, 1032, 1035, 1039, 1040, 1041, 1044 (2 year), 1045, 1046,1064, 1068, 1069 (2 year), 1073, 1109, 1129, 1130, 1152, 1187 and 1237.
Data-lock point: 02MAR2017.
Abbreviations: BID = twice daily; CI = confidence interval; CV = cardiovascular risk factor; HDL = high density lipoprotein; IR = incidence rate; LTE = long-term extension; n = number of patients with events; N= total number of patients; PY = patient-years; RA = rheumatoid arthritis.
Source: Module 5.3.5.3 Safety Table 315a.7.3.1.3; Table 315a.7.3.2.3.

Co-variate analyses in study 1133 and non-1133 RA studies

The MAH provided analyses to identify possible risk factors for DVT and PE in patients using tofacitinib based on clinical trial data of RA study 1133, supported by data from non-1133 RA studies. Risk factors in PsA, PsO and UC patients could not be identified due to the low number of events of PE and DVT in these indications.

Based on these analyses and assessment of the literature, the following risk factors were identified for thromboembolism (VTE): Baseline use of oestrogen replacement therapy, age (≥60 years), obesity (BMI ≥ 30 kg/m^2), baseline antidepressant use, baseline aspirin use, baseline use of oral contraceptives, previous heart failure, previous VTE (either PE or DVT), and smoking. Overall, these risk factors are in line with common knowledge, except for baseline antidepressant use, where the causative role of antidepressant use is not well understood. Obesity (BMI≥30 kg/m^2) was considered as the most prevalent (about 40% of the population in study 1133) and the strongest of the individual differential risk factors.

In RA study 1133 that was 'CVD enriched', most but not all patients had at least one risk factor for PE/DVT. In the table below the results for anti-TNF, tofacitinib 5 mg BID and 10 mg BID are presented, for DVT, PE, AT and death, stratified by presence (left side) or absence (right side) of one or more risk factors for PE/DVT. The results show that in patients with at least one risk factor for PE/DVT, the risk for DVT is increased about 1.5-fold for 5 mg BID and about 2-fold for 10 mg BID, as compared to anti-TNF. Similarly, the risk for PE is increased about 4-fold for 5 mg BID and about 9-fold for 10 mg BID, as compared to anti-TNF. In patients without risk factors for PE/DVT, occurrence of DVT and of PE at follow-up was seldom but the groups were relatively small. Mortality also was numerically raised in the 10 mg BID group more than in the 5 mg BID group and also more than in anti-TNF treated patients.

Table 5 - Number of Subjects with Events and Incidence Rates for Events by Presence or Absence of PE/DVT Risk Factor (A3921133)

	With PE/DVT Risk Factor					**Without PE/DVT Risk Factor**				
Treatment Group	**n/N**	**Patient Years**	**Incidence Rate (95% CI)**	**Treatment Comparison**	**Hazard Ratio (95% CI)**	**n/N**	**Patient Years**	**Incidence Rate (95% CI)**	**Treatment Comparison**	**Hazard Ratio (95% CI)**
Deep Vein Thrombosis*										
Tofa 5 mg BID	10/1257	2852.17	0.35 (0.17, 0.64)	5mg vs TNFi	1.63 (0.59, 4.50)	0/201	464.20	0.00 (0.00,0.79)	5mg vs TNFi	NE (-, -)
Tofa 10 mg BID	12/1224	2598.71	0.46 (0.24, 0.81)	10mg vs TNFi	2.17 (0.81, 5.77)	0/229	533.46	0.00 (0.00,0.69)	10mg vs TNFi	NE (-, -)
TNFi	6/1240	2809.07	0.21 (0.08, 0.46)	10 mg vs 5 mg	1.31 (0.57, 3.04)	0/211	511.46	0.00 (0.00,0.72)	10 mg vs 5 mg	NE (-, -)
Pulmonary Embolism*										
Tofa 5 mg BID	8/1257	2853.05	0.28 (0.12, 0.55)	5mg vs TNFi	3.92 (0.83,18.48)	1/201	464.06	0.22 (0.01,1.20)	5mg vs TNFi	1.05 (0.07,16.75)
Tofa 10 mg BID	17/1224	2589.31	0.66 (0.38, 1.05)	10mg vs TNFi	9.14 (2.11,39.56)	0/229	533.46	0.00 (0.00,0.69)	10mg vs TNFi	NC (0.00, Inf.
TNFi	2/1240	2807.29	0.07 (0.01, 0.26)	10 mg vs 5 mg	2.35 (1.02, 5.45)	1/211	511.46	0.20 (0.00,1.09)	10 mg vs 5 mg	NC (0.00, Inf.
Arterial Thrombotic Embolism*										
Tofa 5 mg BID	20/1257	2845.66	0.70 (0.43, 1.09)	5mg vs TNFi	0.98 (0.52, 1.81)	1/201	462.54	0.22 (0.01,1.20)	5mg vs TNFi	NC (0.00, Inf.)
Tofa 10 mg BID	21/1224	2583.91	0.81 (0.50, 1.24)	10mg vs TNFi	1.13 (0.61, 2.09)	2/229	530.95	0.38 (0.05,1.36)	10mg vs TNFi	NC (0.00, Inf.)
TNFi	20/1240	2788.00	0.72 (0.44, 1.11)	10 mg vs 5 mg	1.17 (0.63, 2.16)	0/211	511.46	0.00 (0.00,0.72)	10 mg vs 5 mg	1.70 (0.15,18.80)

	With PE/DVT Risk Factor					Without PE/DVT Risk Factor				
Treatment Group	**n/N**	**Patient Years**	**Incidence Rate (95% CI)**	**Treatment Comparison**	**Hazard Ratio (95% CI)**	**n/N**	**Patient Years**	**Incidence Rate (95% CI)**	**Treatment Comparison**	**Hazard Ratio (95% CI)**
Mortality (28 Day IR Algorithm)*										
Tofa 5 mg BID	19/1257	2859.74	0.66 (0.40, 1.04)	5mg vs TNFi	2.08 (0.94, 4.59)	0/201	464.20	0.00 (0.00,0.79)	5mg vs TNFi	NE (-, -)
Tofa 10 mg BID	26/1224	2606.84	1.00 (0.65, 1.46)	10mg vs TNFi	3.10 (1.45, 6.62)	2/229	533.46	0.37 (0.05,1.35)	10mg vs TNFi	NC (0.00, Inf.)
TNFi	9/1240	2811.81	0.32 (0.15, 0.61)	10 mg vs 5 mg	1.49 (0.83, 2.70)	0/211	511.46	0.00 (0.00,0.72)	10 mg vs 5 mg	NC (0.00, Inf.)
Mortality (All)**										
Tofa 5 mg BID	29/1257	3604.02	0.80 (0.54, 1.16)	5mg vs TNFi	1.14 (0.67, 1.94)	1/201	582.81	0.17 (0.00,0.96)	5mg vs TNFi	1.04 (0.06,16.61)
Tofa 10 mg BID	42/1224	3398.55	1.24 (0.89, 1.67)	10mg vs TNFi	1.75 (1.06, 2.87)	3/229	668.57	0.45 (0.09,1.31)	10mg vs TNFi	2.70 (0.28,25.93)
TNFi	25/1240	3538.52	0.71 (0.46, 1.04)	10 mg vs 5 mg	1.53 (0.95, 2.46)	1/211	601.02	0.17 (0.00,0.93)	10 mg vs 5 mg	2.60 (0.27,24.98)

CI=Confidence Interval. IR: Incidence Rate (Number of subjects with events per 100 subject-years, naive estimate).
* Total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or death date or to the data cutoff date (28-day algorithm).
**Total follow up time calculated up to the day of the first event, the minimum of subject withdrawal date from study or death date or to the data cutoff date.
n: Number of subjects with the event.
HR=Hazard Ratio. HR and its associated CI were estimated from a Cox regression model including fixed effects of treatment (only the treatment groups involved for the comparison). NC: not calculated, 0 events in one treatment group of the comparison. NE: not estimable, 0 events in both treatment groups of the comparison.
PE risk factor is defined for a subject meeting any of the following criteria: Day 1 use of oral contraceptives or hormone replacement therapy, previous heart failure, previous venous thromboembolism (DVT or PE), age >=60 years, BMI >= 30 kg/m2, smoking, Day 1 antidepressant use, or Day 1 aspirin use.
Datalock Point: 22FEB2019

Similar analyses were performed in the non-1133 RA data (table below), where anti-TNF was not available as long term comparator and in which patients had not been included based on presence of risk factors for CVD. It shows that in patients with at least one risk factor for PE/DVT, the occurrence (IR) of DVT and of PE does not appear to be dissimilar or increasing in a dose dependent way, for 5 mg BID and for 10 mg BID. Mortality appears to be numerically higher in the 5 mg BID group and lower in the 10 mg BID group (in contrast to study 1133).

Table 6 - Number of Subjects with Events and Incidence Rates for Events by Presence or Absence of PE/DVT Risk Factor (RA – P123LTE)

Treatment Group*	With PE/DVT Risk Factor			Without PE/DVT Risk Factor		
	n/N	**Patient Years**	**Incidence Rate (95% CI)**	**n/N**	**Patient Years**	**Incidence Rate (95% CI)**
Deep Vein Thrombosis						
Tofacitinib 5 mg BID	12/1971	5047.11	0.24 (0.12, 0.42)	1/1095	3333.43	0.03 (0.00, 0.17)
Tofacitinib 10 mg BID	18/2623	9417.61	0.19 (0.11, 0.30)	5/1372	5593.09	0.09 (0.03, 0.21)
Tofacitinib 5 & 10 mg BID	30/4594	14464.72	0.21 (0.14, 0.30)	6/2467	8926.52	0.07 (0.02, 0.15)
Pulmonary Embolism						

Treatment Group*	With PE/DVT Risk Factor			Without PE/DVT Risk Factor		
	n/N	Patient Years	Incidence Rate (95% CI)	n/N	Patient Years	Incidence Rate (95% CI)
Tofacitinib 5 mg BID	8/1971	5061.36	0.16 (0.07, 0.31)	0/1095	3334.03	0.00 (0.00, 0.11)
Tofacitinib 10 mg BID	16/2623	9427.16	0.17 (0.10, 0.28)	4/1372	5594.07	0.07 (0.02, 0.18)
Tofacitinib 5 & 10 mg BID	24/4564	14488.52	0.17 (0.11, 0.25)	4/2467	8928.10	0.04 (0.01, 0.11)
Arterial Thrombotic Embolism						
Tofacitinib 5 mg BID	24/1971	5047.63	0.48 (0.30, 0.71)	4/1095	3325.78	0.12 (0.03, 0.31)
Tofacitinib 10 mg BID	47/2623	9318.44	0.50 (0.37, 0.67)	9/1372	5575.37	0.16 (0.07, 0.31)
Tofacitinib 5 & 10 mg BID	71/4594	14366.07	0.49 (0.39, 0.62)	13/2467	8901.15	0.15 (0.08, 0.25)
MACE						
Tofacitinib 5 mg BID	29/1805	4505.51	0.64 (0.43, 0.92)	2/1031	3082.52	0.06 (0.01, 0.23)
Tofacitinib 10 mg BID	40/2474	9240.23	0.43 (0.31, 0.59)	14/1307	5511.81	0.25 (0.14, 0.43)
Tofacitinib 5 & 10 mg BID	69/4279	13745.73	0.50 (0.39, 0.64)	16/2338	8594.33	0.19 (0.11, 0.30)
Mortality (28 Day IR Algorithm)						
Tofacitinib 5 mg BID	26/1971	5080.69	0.51 (0.33, 0.75)	3/1095	3334.03	0.09 (0.02, 0.26)
Tofacitinib 10 mg BID	25/2623	9434.40	0.26 (0.17, 0.39)	5/1372	5598.74	0.09 (0.03, 0.21)
Tofacitinib 5 & 10 mg BID	51/4594	14515.08	0.35 (0.26, 0.46)	8/2467	8932.77	0.09 (0.04, 0.18)
Mortality (All)**						
Tofacitinib 5 mg BID	54/1971	5080.69	1.06 (0.80, 1.39)	10/1095	3334.03	0.30 (0.14, 0.55)
Tofacitinib 10 mg BID	43/2623	9434.40	0.46 (0.33, 0.61)	11/1372	5598.74	0.20 (0.10, 0.35)
Tofacitinib 5 & 10 mg BID	97/4594	14515.08	0.67 (0.54, 0.82)	21/2467	8932.77	0.24 (0.15, 0.36)

*All treatment groups are average daily dose of tofacitinib
**All events are included even those beyond the risk period.
Abbreviations: CI=Confidence Interval; IR=Incidence Rate (N with events per 100 subject-years); n=Number with the event; N=total number of subjects.
Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
PE/DVT risk factor is defined for a subject meeting any of the following criteria: Day 1 use of oral contraceptives or estrogen replacement therapy, previous heart failure, previous venous thromboembolism (DVT or PE), age >=60 years, BMI >= 30 kg/m2, smoking, Day 1 antidepressant use, or Day 1 aspirin use.
Includes Protocols - A392-1019, 1024, 1025, 1032, 1035, 1039, 1040, 1041, 1044 (2yr), 1045, 1046, 1064, 1068, 1069 (2yr), 1073, 1129, 1152, 1187 and 1237
Data-lock point: 02MAR2017

In the non-1133 RA studies, occurrence of events is lower in patients without a risk factor for PE/DVT and the few events of PE and DVT that occurred were all in the 10 mg BID group. Hazard ratios (HR) (95%CI) were not provided. In PsA, PsO and UC it appears that most cases of PE/DVT occurred in patients with at least one risk factor for PE or DVT. In UC patients PE and DVT were observed during prolonged tofacitinib exposure (range 217 up to 1149 days), once remission has been achieved.

The influence of individual risk factors for PE/DVT was analysed, based on review of data from external literature and analysis of the data of study 1133. Obesity, baseline aspirin, baseline anticoagulants and baseline antidepressants were selected as risk factors operational in the database of study 1133. The

effect of tofacitinib dose (5mg BID versus 10 mg BID) was studied conditional on presence/absence of these individual risk factors. Based on frequency of occurrence and effect size, obesity was considered as a good example. The occurrence of PE is clearly raised in patients treated with 10 mg BID in presence of obesity, while there is no apparent difference between the two doses in absence of obesity (table below). Results for baseline aspirin use, baseline anticoagulants, antidepressants, showed similar tendency.

Table 7 - Effect of Obesity on the Rate of Pulmonary Embolism in Tofacitinib Study A3921133 (All Events for Full Follow-up Period)

Tofacitinib Dose	BMI < 30 kg/m²		BMI ⩾ 30 kg/m²		BMI
	PE Events PY	IR (95% CI)	PE Events PY	IR (95% CI)	HR (95% CI) of BMI>=30 versus <30 kg/m2
5 mg BID	6 2472.6	0.25 (0.11, 0.54)	3 1705.5	0.18 (0.06, 0.55)	0.74 (0.18, 2.94)
10 mg BID	6 2411.4	0.25 (0.11, 0.55)	15 1629.0	0.92 (0.56, 1.53)	3.72 (1.44, 9.60)
					Interaction p-Value
HR (95% CI) of 10 mg BID versus 5 mg BID		1.02 (0.33, 3.18)		5.27 (1.53, 18.19)	0.056

Abbreviations: BID = twice daily; BMI = body mass index; CI = confidence interval; HR = hazard ratio; IR = incidence rate; PE = pulmonary embolism; PY = patient years.
Effect of Dose depends on obesity; effect of obesity depends on dose p = 0.056
Proportion of patients with BMI ≥ 30 kg/m2 in Study A3921133 = 40.5%
All events on- and off-treatment are included
Data lock point 22FEB2019

Obesity is a well-known risk factor for venous thromboembolism[2]. The association between the occurrence of PE and the use of aspirin and anticoagulants at baseline is probably at least partly explained by the underlying conditions for which these medications are used. The relation between the use of antidepressants and the occurrence of VTE is unclear.

In conclusion, tofacitinib increases the risk of VTE as compared to treatment with TNFi in patients with known risk factors for VTE (and not to the same extent in patients without such risk factors). The risk for PE is especially raised in presence of these risk factors if 10 mg BID was used, rather than 5 mg BID. It is considered that these risk factors (i.e. use of aspirin and anticoagulants and use of antidepressants) are indicators of the underlying PE risk and useful to analyse the effect of tofacitinib on PE/DVT in presence of PE risk factors. The PRAC didn't consider being useful to try to generalise the risk factors found in this study (i.e. aspirine use/anticoagulant use, antidepressant use) to the target population. Instead, for generalisation and SmPC recommendations it should be relied on external scientific knowledge about known risk factors for PE/DVT. The reason for the above is that the database is considered too small to overrule scientific knowledge from external sources about predictors for VTE events (risk factors such as previous PE, obesity, increasing age etc.) for PE/DVT.

Post marketing safety data on thromboembolic events

In total, 162 cases reporting thromboembolic events (DVT and PE) were identified from global post-marketing sources and non-interventional trials with a data lock point (DLP) of 26 February 2019. Post-marketing cases of PE/DVT have been reported for all indications and treatment regimens, but the majority of the cases is reported in patients with RA (n=120). The majority of post-marketing cases were reported in patients over 50 years of age, which may be expected considering the majority of

[2] Anderson FA & Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-I16.

cases (n=120) was reported for the RA indication. Indication was unknown in approximately a quarter of cases (n=39). Only a few cases were reported for the UC (n=2; both 10 mg BID dosing) and PsA (n=1; 5 mg once daily) indications. Regarding the time to onset (TTO), clinical trial cases showed a relatively long TTO (on average >1 year), whereas post-marketing cases were reported shorter after initiation of tofacitinib treatment (<6 months).

The majority of post-marketing cases contained limited information (i.e. missing information about TTO, risk factors, medical history, etc), precluding causality assessment. In 5 cases, the temporal relationship was considered unlikely, as the event occurred either before tofacitinib initiation or less than 2 days into treatment. The remaining cases were reported in patients with one or more risk factors for PE/DVT. Causality between tofacitinib and the events is therefore difficult to assess based on individual case narratives however it appears that risk factors for thrombotic events are often present. This is in line with the finding of 1133 study where the risk for PE with tofacitinib as compared to TNFi was particularly increased in patients with known DVT/PE risk factors.

2.4.2. Mortality

In Study A3921133, taking into account events up to 28 days after the last dose, overall mortality rates were clearly increased by 2-3 fold for tofacitinib as compared to active control TNFi in a dose dependent way (see Table 8 below). The data have been updated up to the 1st of August 2019, but the patients originally receiving tofacitinib 10 mg had been reallocated to 5 mg since the 22th of February (Table 9), thus limiting the interpretation of the updated data for the tofacitinib 10 mg treatment arm.

When taking into account extended observation periods (i.e. not limited to 28 days) after the last dose in the same study (1133), the mortality rates between randomised to low-dose tofacitinib (5mg BID) and randomised to TNFi were more aligned, although the rate was still significantly higher for the randomised to tofacitinib high-dose (10 mg BID) (Table 9).

In contrast, in the pooled datasets of long-term extension studies of the registration trials of the diverse indications, there was an inverse relationship between mortality and tofacitinib dose.

Table 8 - Overall rates for mortality for study A3921133 (28 day IR algorithm)*

Tofacitinib **5 mg BID** **n/N** **PY** **IR (95% CI)**	**Tofacitinib** **10 mg BID** **n/N** **PY** **IR (95% CI)**	**TNFi** **n/N** **PY** **IR (95% CI)**
Deaths - 28 Day IR Algorithm		
19/1458 3323.95 0.57 (0.34,0.89)	28/1453 3140.31 0.89 (0.59,1.29)	9/1451 3323.27 0.27 (0.12,0.51)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi 10 mg BID to TNFi 10 mg BID to 5 mg BID	2.11 (0.96, 4.67) 3.28 (1.55, 6.95) 1.55 (0.87, 2.78)	

*Only events occurring within 28 days after the last dose or to the data-lock point are included in this table. PY is calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or death date or to the data-lock point. HR and its associated CI were estimated from a Cox regression model including fixed effects of treatment (only the treatment groups involved for the comparison).

Data-lock point: 22FEB2019.

Abbreviations: BID = twice daily; CI = confidence interval; CV = cardiovascular risk factor; HDL = high density lipoprotein; HR = hazard ratio; IR = incidence rate; LTE = long-term extension; n = number of patients with events; N= total number of patients; PY = patient-years; RA = rheumatoid arthritis, TNFi = tumour necrosis factor inhibitor.

In study 1133, the incidence rates for mortality (28-day algorithm) in study 1133 were the lowest for patients treated with anti-TNF, and were relatively increased for patients treated with 5 mg BID or treated with 10 mg BID (Tables 8 and 9). Only the increase in 10 mg is statistically significant, however the non-statistically trend for increase in the 5 mg group is considered as clinically relevant which is supported by the evidence of a dose-response relationship. In comparison to the previously submitted data the incidence rates (number of cases/observation time) changed numerically and the relative differences (HR) of tofacitinib 5 mg and 10 mg as compared to anti-TNF became less extreme. Updated data up to 22 February 2019 (i.e. before patients on 10 mg were switched to 5 mg) has been provided (Table 10).

If the observation period is lengthened beyond the period of exposure (using the 90-day algorithm or the full period) findings are consistent, though the differences attenuate. Because of the latter, the 28-day period is considered most relevant.

Table 9 - Overall All-Cause Mortality Incidence Rates for Study A3921133, updated to 1st August 2019

Tofacitinib 5 mg BID **n/N** **PY** **IR (95% CI)**	**Tofacitinib 10 mg BID** **n/N** **PY** **IR (95% CI)**	**TNFi** **n/N** **PY** **IR (95% CI)**
Deaths - 28 Day IR Algorithm*[a]		
23/1458 3714.81 0.62 (0.39, 0.93)	35/1453 3894.98 0.90 (0.63, 1.25)	18/1452 3706.78 0.49 (0.29, 0.77)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi 10 mg BID to TNFi 10 mg BID to 5 mg BID	1.31 (0.71, 2.42) 1.89 (1.07, 3.34) 1.45(0.86, 2.45)	
Deaths – 90 Day IR Algorithm[b]		
29/1458 3898.17 0.74 (0.50,1.07)	45/1453 4127.23 1.09 (0.80,1.46)	23/1452 3884.32 0.59 (0.38,0.89)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi 10 mg BID to TNFi 10 mg BID to 5 mg BID	1.28 (0.74, 2.21) 1.85 (1.12, 3.05) 1.46 (0.91, 2.32)	
Deaths – All Exposure		
36/1458 4692.50 0.77 (0.54, 1.06)	53/1453 4547.61 1.17 (0.87, 1.52)	33/1452 4656.22 0.71 (0.49, 1.00)
Pairwise comparisons	**HR (95% CI)**	
5 mg BID to TNFi 10 mg BID to TNFi 10 mg BID to 5 mg BID	1.08 (0.68, 1.74) 1.64 (1.06, 2.54) 1.52 (0.99, 2.32)	

Source: Module 5.3.5.3 Safety Table 1597.3.1, Table 1597.3.2, Table 1597.3.3.
*Only events occurring within 28 days after the last dose or to the data-cutoff are included.
[a] PY is calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or death date or to the data-cutoff.
[b] PY is calculated up to the day of the first event, subject to a risk period of up to 90days beyond the last dose or death date or to the data-cutoff.
HR and its associated CI were estimated from a Cox regression model including fixed effects of treatment (only the treatment groups involved for the comparison).
Subjects randomized to tofacitinib 10 mg BID were switched to 5 mg BID after the data cutoff of 22FEB2019. For these subjects, all events regardless whether the events occurred while subjects receiving tofacitinib 10 mg BID or 5 mg BID were analyzed in the randomized treatment group of tofacitinib 10 mg BID.
Data-cutoff: 01AUG2019.
Abbreviations: BID = twice daily; CI = confidence interval; HR = hazard ratio; IR = incidence rate; n = number of patients with events; N= total number of patients; PY = patient-years; TNFi = tumour necrosis factor inhibitor.

Table 10 - Rates for mortality for study A3921133 (28 day IR algorithm), cut-off at 22 February

Cause of Death	Treatment Group	N	n	%	PY	IR (95% CI)	Treatment Comparison	IR Ratio (95% CI)
Deaths - Cardiovascular Events	Tofacitinib 5 mg BID	1458	8	0.55	3323.95	0.24 (0.10, 0.47)	Tofa 5 mg vs TNFi	1.14 (0.36, 3.70)
	Tofacitinib 10 mg BID	1453	14	0.96	3140.31	0.45 (0.24, 0.75)	Tofa 10 mg vs TNFi	2.12 (0.80, 6.20)
	TNFi	1451	7	0.48	3323.27	0.21 (0.08, 0.43)		
Deaths - Infections	Tofacitinib 5 mg BID	1458	6	0.41	3323.95	0.18 (0.07, 0.39)	Tofa 5 mg vs TNFi	3.00 (0.54, 30.39)
	Tofacitinib 10 mg BID	1453	7	0.48	3140.31	0.22 (0.09, 0.46)	Tofa 10 mg vs TNFi	3.70 (0.71, 36.54)
	TNFi	1451	2	0.14	3323.27	0.06 (0.01, 0.22)		
Deaths - Other Causes	Tofacitinib 5 mg BID	1458	1	0.07	3323.95	0.03 (0.00, 0.17)	Tofa 5 mg vs TNFi	NE
	Tofacitinib 10 mg BID	1453	5	0.34	3140.31	0.16 (0.05, 0.37)	Tofa 10 mg vs TNFi	NE
	TNFi	1451	0	0.00	3323.27	0.00 (0.00, 0.11)		

Over the complete period of follow-up for study 1133, for a comparable number of subjects exposed (N) the raw numbers of deaths (n) reflects again the higher mortality rates in the tofacitinib groups as compared to anti-TNF (Table 11). Regarding death causes, in the tofacitinib 5 mg and 10 mg groups, more patients died due to an infection as compared to anti-TNF: respectively n=8 and n=9 versus n=4. Cardiovascular deaths were more apparent in the tofacitinib 10 mg group, as compared to 5 mg and anti-TNF: respectively n=17 versus n=9 and n=10. In the individual death cause listings, only two deaths were labelled and adjudicated as due to PE. The findings were consistent when the observation period was extended.

Table 11 - Summary of Overall Causes of Deaths by 6-Month Intervals (A3921133) (28 Day IR Algorithm)

Reason of Death	Treatment Group	N	n	%*
All Deaths	Tofa 10mg BID	2	0	0.00
	TNFi	8	0	0.00
All Deaths	Tofa 5mg BID	1458	23	1.58
	Tofa 10mg BID	1453	35	2.41
	TNFi	1452	18	1.24
Deaths - Infections	Tofa 5mg BID	1458	8	0.55
	Tofa 10mg BID	1453	9	0.62
	TNFi	1452	4	0.28
Deaths - Cardiovascular Events	Tofa 5mg BID	1458	9	0.62
	Tofa 10mg BID	1453	17	1.17
	TNFi	1452	10	0.69
Deaths - Other Causes	Tofa 5mg BID	1458	2	0.14
	Tofa 10mg BID	1453	7	0.48
	TNFi	1452	3	0.21

The occurrence of fatal serious infections is almost similar in the 5 mg and 10 mg groups with an IR of ~0.28, which is double the IR of 0.13 in the anti-TNF group (Table 12), again not statistically significant.

Table 12 - Serious Fatal Infection Incidence Rate (IR = Number of Patients with Events per 100 Patient Years) in Study A3921133

Treatment	n/N	Patient Years	IR (95% CI)	Treatment Comparison	HR (95% CI)
28 Day IR Algorithm[a]					
Tofacitinib 5 mg BID	10/1458	3711.62	0.27 (0.13,0.50)	Tofa 5mg vs TNFi	2.02(0.69, 5.90)
Tofacitinib 10 mg BID	11/1453	3891.21	0.28 (0.14,0.51)	Tofa 10mg vs TNFi	2.11(0.73, 6.06)
TNF Inhibitor	5/1452	3705.82	0.13 (0.04,0.31)	Tofa 10 mg vs 5 mg	1.07(0.45, 2.51)
All Events for Full Period[b]					
Tofacitinib 5 mg BID	10/1458	4687.78	0.21 (0.10, 0.39)	Tofa 5mg vs TNFi	1.66(0.60, 4.56)
Tofacitinib 10 mg BID	12/1453	4543.59	0.26 (0.14, 0.46)	Tofa 10mg vs TNFi	2.04(0.76, 5.43)
TNF Inhibitor	6/1452	4655.04	0.13 (0.05, 0.28)	Tofa 10 mg vs 5 mg	1.22(0.53, 2.83)

BID = twice daily, CI = confidence interval, IR = incidence rate; N = number of patients in each treatment group; n = number of patients with an event; PY = patient-years of observation; HR = hazard ratio, TNF = tumour necrosis factor, TNFi = tumour necrosis factor inhibitor.
Patients randomized to tofacitinib 10 mg BID were mandatorily switched to tofacitinib 5 mg BID after the 22Feb2019 datacut. The data collected before and after the dose switch from these patients were analyzed in their randomized treatment group, tofacitinib 10 mg BID.
[a] Only events occurring within 28 days after the last dose or to the data cutoff are included. PY: Total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or death date or to the data cutoff date (28-day algorithm).
[b] All events on- and off-treatment are included. PY: Total follow up time calculated up to the day of the first event, the minimum of patient withdrawal date from study or death date or to the data cutoff date.
Data cutoff 01AUG2019

In study 1133, it appears that non-fatal serious infections occur more frequently in the tofacitinib 5 mg and 10 mg groups as compared to anti-TNF (Table 13), although the increases (HR) are not statistically significant.

Table 13 - Non-fatal Serious Infection Incidence Rate (IR = Number of Patients with Events per 100 Patient Years) in Study A3921133

Treatment	n/N	Patient Years	IR (95% CI)	Treatment Comparison	HR (95% CI)
28 Day IR Algorithm[a]					
Tofacitinib 5 mg BID	120/1458	3582.77	3.35 (2.78,4.01)	Tofa 5mg vs TNFi	1.20(0.92, 1.56)
Tofacitinib 10 mg BID	131/1453	3735.99	3.51 (2.93, 4.16)	Tofa 10mg vs TNFi	1.27(0.98, 1.64)
TNF Inhibitor	102/1452	3649.54	2.79 (2.28, 3.39)	Tofa 10 mg vs 5 mg	1.05(0.82, 1.35)
All Events for Full Period[b]					
Tofacitinib 5 mg BID	128/1458	4458.49	2.87 (2.40, 3.41)	Tofa 5mg vs TNFi	1.15(0.89, 1.48)
Tofacitinib 10 mg BID	141/1453	4303.14	3.28 (2.76, 3.86)	Tofa 10mg vs TNFi	1.31(1.02, 1.67)
TNF Inhibitor	112/1452	4476.05	2.50 (2.06, 3.01)	Tofa 10 mg vs 5 mg	1.14(0.90, 1.45)

BID = twice daily, CI = confidence interval, IR = incidence rate; N = number of patients in each treatment group; n = number of patients with an event; PY = patient-years of observation; HR = hazard ratio, TNF = tumour necrosis factor, TNFi = tumour necrosis factor inhibitor.
Patients randomized to tofacitinib 10 mg BID were mandatorily switched to tofacitinib 5 mg BID after the 22Feb2019 data cutoff. The data collected before and after the dose switch from these patients were analyzed in their randomized treatment group, tofacitinib 10 mg BID.
[a] Only events occurring within 28 days after the last dose or to the data cutoff are included. PY: Total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or death date or to the data cutoff date (28-day algorithm).
[b] All events on- and off-treatment are included. PY: Total follow up time calculated up to the day of the first event, the minimum of subject withdrawal date from study or death date or to the data cutoff date.
Data cutoff 01AUG2019

In the studies other than RA study 1133 in RA, PsO, PsA and UC, when looking at the 'full randomized period up to 24 months' (Table 14), it appears that more deaths occur in the groups treated with tofacitinib 5 mg as compared to 10 mg. Though numbers of deaths are low, similar trend is reflected in the number of deaths occurring in PsO (n=3 for 5 mg and n=1 for 10 mg) and PsA (n=1 for 5 mg and n=0 for 10 mg), while no death occurred in UC. Over the disease groups (RA, PsO, PsA, UC) the exposure to 5 mg and 10 mg is balanced, though most data come from RA followed by psoriasis.

Table 14 - Overall Mortality Incidence Rates and Hazard Ratios/Incidence Rate Differences for Placebo-Controlled and Active-Controlled Phases of Randomized Clinical Trials (RCTs) Across Indications (28-Day IR Algorithm)[*]

Cohort	Study Dosing	RA n/N PY IR (95% CI)	PsO n/N PY IR (95% CI)	PsA n/N PY IR 95% CI	UC n/N PY IR 95% CI
Full Randomized Period 0-24 Months[g]	**5 mg BID**	8/2664 2584.41 0.31 (0.13,0.61)[b]	3/1217 893.16 0.34 (0.07, 0.98)[c]	1/347 201.10 0.50 (0.01, 2.77)	0/198 148.77 0.00 (0.00, 2.48)[d]
	10 mg BID	4/2024 1998.65 0.20 (0.05,0.51)[b]	1/1219 960.99 0.10 (0.00, 0.58)[c]	0/344 197.23 0.00 (0.00, 1.87)	0/196 157.31 0.00 (0.00, 2.35)[d]
	Placebo	1/1136 311.25 0.32 (0.01,1.79)[b]	NA	NA	0/198 103.42 0.00 (0.00, 3.57)[d]
	Adalimumabe	1/643 554.37 0.18 (0.00,1.01)[b]	NA	0/106 92.62 0.00 (0.00, 3.98)	NA
	Methotrexatef	0/223 301.42 0.00 (0.00,1.22)[b]	NA	NA	NA
	Pairwise comparison	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**IR Difference (95% CI)**
	Tofacitinib 5 mg BID to Placebo Tofacitinib 10 mg BID to Placebo Tofacitinib 10 mg BID to 5 mg BID	0.12 (0.00, 3.48) 0.27 (0.02, 3.64) 0.56 (0.16, 1.91)	NA NA 0.31 (0.03, 3.03)	NA NA NC	0.00 (0.00, 0.00) 0.00 (0.00, 0.00) 0.00 (0.00, 0.00)

*Only events occurring within 28 days after the last dose are included in this table unless noted otherwise. PY is the time to the event or to the last dose date + 28 days unless noted otherwise. Rates = events/100 patient years (all events).
[a] For UC Placebo Period, the duration was 2 months.
[b] For RA Full Randomized Period, events are counted within 28 days after the last dose and PY is the time to the event or to the last dose date.
[c] For PsO Full Randomized Period, all events are counted and PY is the time to the event or to the last dose date. 95% CI for IR was not calculated
[d] For UC Full Randomized Period, there was placebo data for the full randomized period (52 week duration study A3921096). There was no placebo data for RA, PsO, or PsA full randomized periods. Placebo data for RA and PsO programs is limited to 0-3 months.
[e] Adalimumab data is from RA Study A3921064 (1-year duration) and PsA Study A3921091 (1 year duration).
[f] MTX data is from RA Study A3921069 (2-year duration)
Rates = number of patients with events/100 patient years.
[g] RA RCTs = P2P3 (0-24 months); PsO RCTs = P3 (0-12 months); PsA RCTs = P3 (0-12 months); UC RCTs = P3 (0-12 months).
Abbreviations: BID = twice daily; CI = confidence interval; HR = hazard ratio; IR = incidence rate; n = number of patients with events; N = total number of patients; NA =not applicable; NC = not calculated; NE = not estimable due to 0 event in at least one treatment group in a comparison; PsA = psoriatic arthritis; PsO = psoriasis; PY = patient-years; RA = rheumatoid arthritis; RCT = randomized clinical trials; UC = ulcerative colitis.

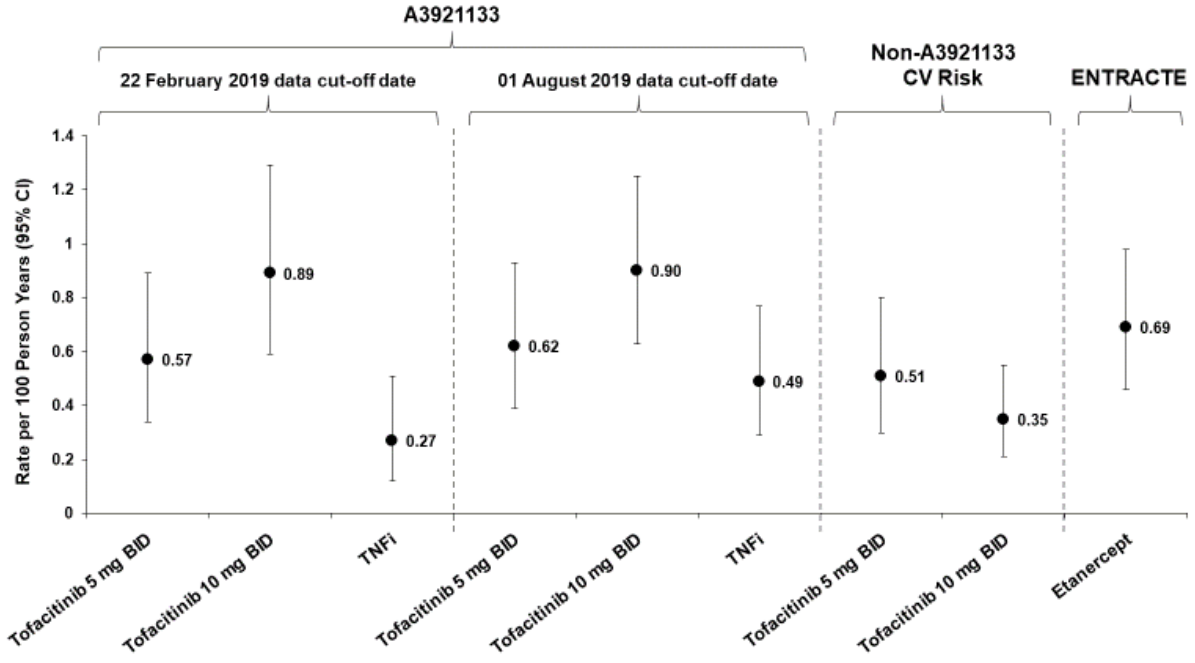
To put mortality data of tofacitinib treated patients in context, the MAH identified one published RCT that was similar to the 1133 study (ENTRACTE) and provided data from the CORRONA registry.

ENTRACTE was a randomised-controlled trial, to compare the risk for MACE among RA patients treated with tocilizumab or etanercept. All-cause mortality was a secondary endpoint. All patients enrolled had high RA disease activity at baseline, were aged ≥50 years, and at baseline had at least one traditional CVD risk factor, extra-articular RA manifestations or history of a CVD event. In addition, an analysis was conducted within the US Corrona Registry database to estimate mortality rates among patients with moderate-to-severe RA, who were ≥ 50 years old and who had at least 1 CV risk factor.

From comparison of the baseline data it can be derived that the populations of study 1133, non-1133 studies, ENTRACTE, and CORRONA are quite similar in demographic variables and in RA- and CVD disease characteristics. The samples can be considered to reflect the same underlying population of RA patients of older age with an increased risk of CVD. The ENTRACTE and CORRONA samples have observation periods of on average 3.2 and overall in CORRONA of 4.4 years, which is considered long enough to study mortality.

The IR for mortality in study 1133 was 0.90 for tofacitinib 10 mg and 0.62 for tofacitinib 5 mg, which was higher than the IR for anti-TNF (0.49), as well as for tofacitinib 5 mg and 10 mg in CV enriched non-1133 (0.51 and 0.35). The IR for mortality in study 1133 was also higher for tofacitinib 10 mg than that for etanercept in ENTRACTE (0.69). The IRs for mortality with extended follow-up of tocilizumab and of etanercept (ENTRACTE) and of biological DMARDs (CORRONA) were higher than was reached for tofacitinib 5 mg and 10 mg in the non-1133 data and the 1133 study.

Figure 1 - Mortality Rates from Drug Initiation to 28 Days After Last Dose : Study A3921133, Non-A3921133 CV Risk Factor-Enriched Patients in Tofacitinib Clinical Studies (RA P123LTE) and Moderate to Severe RA Patients from External Data Source (ENTRACTE)



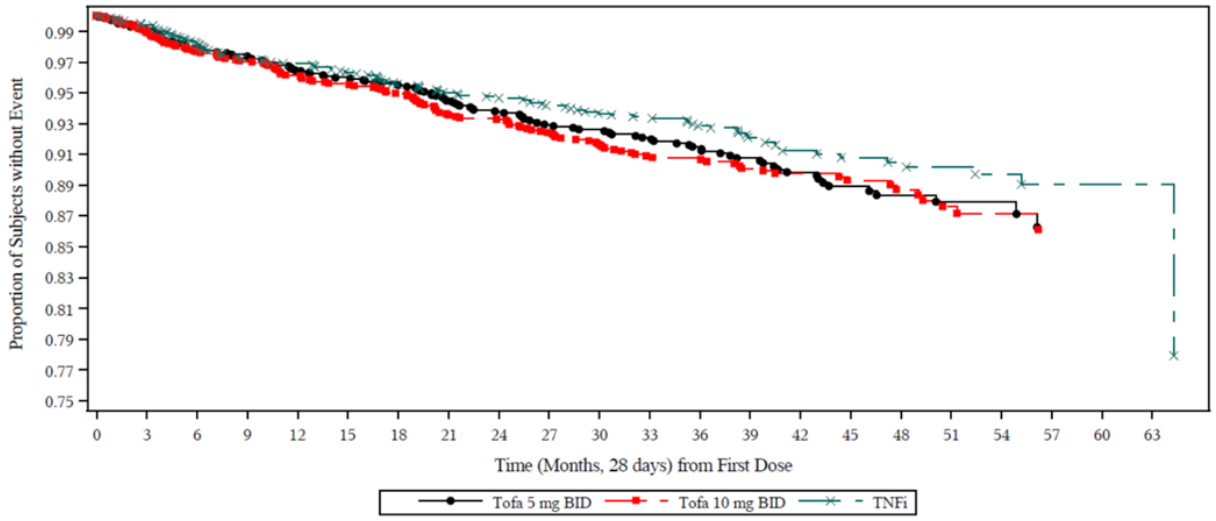
Abbreviations BID=twice daily; CV=cardiovascular; mg=miligrams; RA=rheumatoid arthritis; TNFi = tumour necrosis factor inhibitors

2.4.3. Infections and age

The occurrence of fatal serious infections is about the same in the 5 mg and 10 mg groups with an IR of ~0.28, which is double the IR of 0.13 in the anti-TNF group, while not statistically significant. These

patterns are mirrored in the occurrence of non-fatal serious infections (Figure 2), while the curves of tofacitinib 5 mg and 10 mg tend to overlay and together separate from the curve for anti-TNF.

Figure 2 - Kaplan-Meier Plots of Proportions of Patients without non-Fatal Serious Infections (A3921133) (28-Day IR Algorithm)



For serious infections (fatal and non-fatal), it appears that for tofacitinib 5 mg and 10 mg as well as anti-TNF, the IR is increased for patients ≥65 years of age, as compared to the younger patients, but more so for both tofacitinib groups and more for 10 mg than for 5 mg (Table 15). For both tofacitinib 5 mg and 10 mg the IR steadily increases numerically over age classes with marked increases between 60 and 70 and above. The same trend is visible with anti-TNF, but there the increase is numerically less steep up to ≥75 years of age.

Table 15 - Summary of Incidence Rates by Treatment Group and Age Group for All Serious Infections - A3921133 (Data Cutoff 01AUG2019) (28-Day IR Algorithm)

	Tofa 5 mg BID			Tofa 10 mg BID			TNFi		
Age Group (years)	**N**	**n**	**IR (95% CI)[a]**	**N**	**n**	**IR (95% CI)[a]**	**N**	**n**	**IR (95% CI)[a]**
<55	343	24	2.80 (1.79, 4.16)	310	16	1.86 (1.07, 3.03)	334	18	2.05 (1.21, 3.23)
55-<60	375	24	2.53 (1.62, 3.76)	369	22	2.17 (1.36, 3.28)	372	26	2.76 (1.81, 4.05)
60-<65	349	32	3.70 (2.53, 5.23)	327	37	4.44 (3.13, 6.12)	313	18	2.28 (1.35, 3.60)
65-<70	243	21	3.57 (2.21, 5.46)	282	42	6.10 (4.40, 8.25)	232	17	2.99 (1.74, 4.79)
70-<75	102	18	8.21 (4.87, 12.97)	102	18	8.21 (4.87, 12.98)	133	16	5.02 (2.87, 8.15)
≥75	46	11	10.91 (5.44, 19.52)	63	7	6.00 (2.41, 12.36)	68	12	7.89 (4.07,13.77)

*Subjects randomized to tofacitinib 10 mg BID were mandatorily switched to tofacitinib 5 mg BID after the 22Feb2019 datacut. The data collected before and after the dose switch from these subjects were analyzed in their randomized treatment group, tofacitinib 10 mg BID.
Abbreviations: BID = twice daily; CI = Confidence Interval; IR = Incidence Rate (per 100 PY); N = Number of subjects included in the analysis; n = number of subjects with event; TNFi = Tumor Necrosis Factor inhibitor; Tofa = Tofacitinib.
[a] 95% CI for IR is calculated based on Exact Poisson Distribution.

For mortality (28-day algorithm) it appears that in the younger patients <65 years of age, the IR for mortality seems similar for tofacitinib 5 mg and anti-TNF (Table 16). The IR for mortality is increased in ≥65 years of age for all three medication groups as compared to <65 years of age. The IR for mortality is highest in patients ≥65 years of age on tofacitinib 5 mg (ranging from 0.98 to 2.66) and 10 mg (ranging from 1.23 to 4.20), in a probably dose-dependent way and higher than the IR for anti-TNF (ranging from 0.52 – 1.83). The analysis using the extended observation period points to the same pattern.

Table 16 - Summary of Incidence Rates by Treatment Group and Age Group for Mortality - A3921133 (Data Cutoff 01AUG2019, Data Snapshot 01AUG2019) (28-Day IR Algorithm)

	Tofa 5 mg BID			Tofa 10 mg BID			TNFi		
Age Group (years)	N	n	IR (95% CI)[a]	N	n	IR (95% CI)[a]	N	n	IR (95% CI)[a]
<55	343	3	0.34 (0.07,1.00)	310	3	0.34 (0.07,0.99)	334	0	0.00 (0.00,0.41)
55-<60	375	2	0.20 (0.02,0.74)	369	9	0.87 (0.40,1.64)	372	4	0.42 (0.11,1.07)
60-<65	349	5	0.56 (0.18,1.30)	327	5	0.57 (0.18,1.32)	313	5	0.63 (0.20,1.46)
65-<70	243	6	0.98 (0.36,2.13)	282	9	1.23 (0.56,2.33)	232	3	0.52 (0.11,1.52)
70-<75	102	4	1.73 (0.47,4.42)	102	4	1.70 (0.46,4.35)	133	3	0.92 (0.19,2.70)
≥75	46	3	2.66 (0.55,7.78)	63	5	4.20 (1.36,9.79)	68	3	1.83 (0.38,5.35)

*Subjects randomized to tofacitinib 10 mg BID were mandatorily switched to tofacitinib 5 mg BID after the 22Feb2019 datacut. The data collected before and after the dose switch from these subjects were analyzed in their randomized treatment group, tofacitinib 10 mg BID.
Abbreviations: BID = twice daily; CI = Confidence Interval; IR = Incidence Rate (per 100 PY); N = Number of subjects included in the analysis; n = number of subjects with event; TNFi = Tumor Necrosis Factor inhibitor; Tofa = Tofacitinib.
[a] 95% CI for IR is calculated based on Exact Poisson Distribution.

2.4.4. Discussion on clinical safety data

The available safety data show an increased risk for developing PE (pulmonary embolism) and DVT (deep venous thrombosis) in Rheumatoid Arthritis patients treated with tofacitinib, as compared to TNFi. The risk for these venous thrombo-embolic events is more pronounced in patients with risk factors for VTE and when using the higher 10 mg BID tofacitinib dose instead of the lower 5 mg BID tofacitinib dose. Furthermore, it appears to be a dose-dependent risk.

The strongest evidence comes from the 'CV enriched' study 1133 in about 4650 RA patients, 50 years of age and older, with one or more CV risk factors at baseline, who were randomized to tofacitinib 5 mg BID, tofacitinib 10 mg BID or a TNF-inhibitor (TNFi). For the TNFi group, 3 cases of PE occurred in 1451 patients [IR 0.09 (0.02, 0.26) per 100 PY]. The risk for PE is larger when compared to TNFi in the 10 mg BID group (17 cases out of 1453 patients; IR per 100 PY: 0.54 (0.32-0.87); HR vs. TNFi: 5.96 (1.75-20.33)) followed by the 5 mg BID group (9/1458, IR 0.27 (0.12-0.52) per 100 PY; HR vs. TNFi: 2.99 (0.81, 11.06). The HR of 10 mg BID vs TNFi for PE was 9 in the patients with selected PE/DVT risk factors, and the HR of 5 mg BID versus TNFi was 4 in patients with selected PE/DVT risk factors.

Although the increased risk of PE in the 5 mg group did not reach statistical significance, it is considered clinically relevant, and cannot be seen in isolation from the findings in the 10 mg group. Moreover, the study was not powered *a priori* for thrombotic events. Thus, also for the arthritis indications where the standard dose should not exceed 5 mg BID, the risk of thrombotic events associated with tofacitinib is considered relevant.

For DVT (deep venous thrombosis), the incidence was 6/1451 (IR 0.18 (0.07-0.39) for TNFi, 10/1458 (IR 0.30 (0.14, 0.55)) for tofacitinib 5 mg BID, and 12/1453 (IR 0.38 (0.20, 0.67)) for tofacitinib 10 mg BID. Hazard ratios were statistically non-significant different between treatment groups for the DVT outcome.

Risk factors selected for the 'high risk' subpopulation in study 1133 were based on literature: use of oral contraceptives or oestrogen replacement therapy, previous heart failure, previous venous thromboembolism (DVT or PE), age >=60 years, BMI >= 30 kg/m2, smoking, antidepressant use, aspirin use. From a prognostic analysis for risk factors in the 1133 data, no 'differential' risk factors explaining VTE risk in tofacitinib versus TNF-inhibitor were found. Hence, it is considered that in order to identify a population at high risk for VTE in the SmPC, use should be made of generally known risk factors (Use of combined hormonal contraceptives or hormone replacement therapy, Heart failure,

Previous venous thromboembolism (DVT/PE), Inherited coagulation disorder, Malignancy, Major surgery). Other risk factors as issued by the European Respiratory Society may be considered to evaluate the VTE risk in individual patients, based on their clinical relevance and likely occurrence in the population of patients that may be treated with tofacitinib.

DVT was less often reported than PE in the study, whereas in daily clinical practice, DVT occurs far more often than PE. This might be due to underreporting of DVT, which may occur unnoticed, whereas PE's are serious emergent events requiring immediate hospitalisation. As such, the warnings implemented in the product information address both PE and DVT events, as these cannot be distinguished from a clinical and causal perspective.

The increased risk for PE was also reflected in the numerical results from pre-registration RA studies – though to lesser extent than in Study 1133. A few cases of PE occurred in the smaller PsO, PsA, and UC studies, with a propensity for 10 mg BID.

In contrast to study 1133, no clear signal of thrombotic events was noticed in the pre-registration trials. However, these trials in general included selected populations at low risk of thrombotic events. Moreover, the active comparator groups were small, and the placebo-controlled period was relatively short (RA: 3 months; UC: up to one year), making it difficult to draw conclusions on the risk of uncommon but serious thrombotic events. This could be explained by the fact that cardiovascular compromised patients, as included in study 1133, are more sensitive for these events than patients without cardiac risk factors. This may explain the observed differences between pre-registration cohorts and study 1133. It was apparent that the risk (tofacitinib versus anti-TNF) for PE increased in the subgroup of patients with at least one risk factor for PE.

In UC patients neither PE events nor DVT events were reported for patients treated with tofacitinib 5 mg BID. For tofacitinib10 mg BID the incidence rate of PE was 0.21 (4/960) (95% CI 0.06 - 0.55), and the incidence rate of DVT was 0.05 (1/960) (95% CI 0.00 - 0.30). This observation supports the observed dose dependency.

Limited data on the risk of VTE in UC patients treated with tofacitinib are available. These data however do not indicate an increased risk for DVT/PE in this population with a baseline increased risk of VTE. Moreover, the large increase in the occurrence of these events in RA patients was not observed in UC patients.

It is noted that all patients with moderate to severe UC who developed PE or DVT during tofacitinib treatment were exposed to tofacitinib for more than 200 days. Hence, PE and DVT were observed more frequently upon prolonged tofacitinib exposure.

Risk of VTE is about two times as high in UC patients compared to patients without this disease[3]. Apart from this, the risk of VTE is mediated by general risk factors for VTE such as obesity, history of VTE, advanced age[4]. Available data on the occurrence of VTE indicates that tofacitinib treatment is associated with an increased risk of VTE, especially in patients with risk factors for VTE, and in patients treated with tofacitinib 10 mg BID. It is noted that tofacitinib treatment is only indicated in patients with active RA, PsA, or UC. All PE and DVT cases of VTE in UC patients were observed during tofacitinib maintenance treatment once remission has been achieved. These data indicate that the risk of VTE during tofacitinib treatment might also be influenced by disease activity. Tofacitinib may reduce the absolute risk of VTE in patients with active UC by virtue of its anti-inflammatory properties. Due to the (almost) absence of inflammation in patients with UC in remission, the anti-inflammatory properties of

[3] Yuhara H, Steinmaus C, Corley D, Koike J, Igarashi M, Suzuki T, Mine T. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 May;37(10):953-62. doi: 10.1111/apt.12294. Epub 2013 Apr 2

[4] Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16.

tofacitinib will not compensate for the thrombogenic potential of tofacitinib. This could explain why all observed cases of VTE in UC patients were observed during tofacitinib maintenance treatment at a dosage of 10 mg BID in patients with UC in remission, while no cases of VTE were observed during tofacitinib induction treatment at the same dosage in patients with moderately to severely active UC. Hence, caution for the risk of VTE is especially needed with respect to tofacitinib maintenance treatment in patients with no active disease.

Limited data are available from the PsA target population. It is considered appropriate to extrapolate the safety findings regarding PE and DVT from RA to PsA, since in general auto-immune related arthritis disorders are associated with cardiovascular risks.

Extrapolation from the data from RA patients to UC patients is not straightforward, given differences in aetiology, demographic, disease activity, background treatment and cardiovascular risks in these populations. Thus far, PE (n= 4) and DVT (n=1) were observed in a limited number of UC patients (n=1157). All respective UC patients (n= 938) were treated with tofacitinib 10 mg BID in the induction treatment, during maintenance patients were treated with either 5 mg (n= 197) or 10 mg (n= 960), and all respective patients had risk factors for thromboembolism (e.g. prior PE or DVT, BMI > 30 kg/m^2, long travel after accident). Due to the limited number of thromboembolic events in UC patients, no definite conclusions considering the contribution of the various risk factors can be made. Notwithstanding these differences, it appears that the results, discussion, and conclusions derived from the RA patients can be extrapolated, albeit with some caution. Risk factors for VTE will apply for all indications (RA, PsA and UC), although the occurrence of risk factors (and the underlying background risk) for PE may be different in UC patients due to different demographic, clinical characteristics and comorbidities as well as underlying background VTE risk.

In study 1133, the incidence of death rates (28 Day IR Algorithm) was 9/1451 (IR 0.27 (0.12,0.51) per 100 PY) for TNFi, 19/1458 (IR 0.57 (0.34,0.89) per 100 PY) for tofacitinib 5 mg BID, and 28/1453 (IR 0.89 (0.59,1.29) per 100 PY) for tofacitinib 10 mg BID. Hazard ratios were 2.11 (95% CI 0.96, 4.67) for tofacitinib 5 mg BID to TNFi and 3.28 (95% CI 1.55, 6.95) tofacitinib 10 mg BID. In addition, the survival curves for the three treatments groups do not cross, indicating that there is a difference between treatment groups.

Although no definitive conclusions may be drawn from Study 1133, as this study is still ongoing, the 2-3 fold increased mortality for tofacitinib as compared to TNFi is of concern.

Mortality was mainly due to malignancies, cardiovascular (CV) disorders and infections. The observed dose dependency for lethal infection cases, an established adverse drug reaction, indicates causality. Also of concern is the increased mortality due to CV events by a factor of 2 for the 10 mg BID dose.

In contrast to what is seen in study 1133, in the 'non-1133' RA data there is no trend of increased mortality when comparing 5 mg BID to 10 mg BID treated patients. Though, the contrast in the non-1133 RA studies was less due to the possibility to switch dose. Thus, while a strong signal for a dose-dependent increased mortality with tofacitinib as compared to anti-TNF comes from the 1133 data (patients with RA being >55 years of age and at least one additional CVD risk factor), this is not reflected in 'non-1133' data of RA patients with or without risk factors for CVD or PE. In the PsO, PsA and UC studies there is no tendency that mortality is larger with 10 mg tofacitinib as compared to 5 mg tofacitinib. Comparisons with adalimumab or methotrexate are more difficult to make due to limited exposure in numbers and time, but mortality seems more favourable in adalimumab or methotrexate treated groups as compared to tofacitinib.

In study 1133 the main causes of death (infections, cardiovascular events, and malignancies) are in line with what can be expected in the RA population. Therefore, the between-group contrasts are of interest. In the tofacitinib 5 mg and 10 mg groups, more patients died due to an infection as compared

to anti-TNF, while cardiovascular deaths were more apparent in the tofacitinib 10 mg group, as compared to 5 mg and anti-TNF. Only two deaths were labelled and adjudicated as due to PE. Malignancies as well as 'other causes' were less frequently observed as causes of death. In the non-1133 RA data, the causes of death are consistent with those observed in study 1133. Besides fatal infections, also non-fatal serious infections tend to occur more frequently in the tofacitinib 5 mg and 10 mg groups as compared to anti-TNF.

The MAH has provided an analysis in search for risk factors for mortality in study 1133. A search for 'differential risk factors' specific for tofacitinib did not provide meaningful results, and it seems that the use of 10 mg tofacitinib overrules the influence of other risk factors. As such it should be relied on the generally known risk factors for VTE in order to identify patients at increased risk for PE/DVT as reflected in the updated SmPC recommendations.

No signal of increased mortality was noted in the registration trials and an inverse dose-response relationship was shown in the long-term extension studies of the pre-registration trials. However, study 1133 is a larger scaled, randomised and active controlled study of long-duration, and therefore these outcomes cannot be overlooked. It might be that the study population of Study 1133, with one or more CV risk factors, is more sensitive to not only detect treatment-related effects on thrombotic events, but also on serious infections and CV death. Study 1133 is not-blinded in contrast to the pre-registration trials, but the outcome death is unlikely affected by the open-label design.

There are currently not much data available to put the mortality in study 1133 and 'CV enriched' non-1133 RA studies into context, only one published study (ENTRACTE) and a database (CORRONA) were presented by the MAH. From the cross-study comparison of mortality rates it can be derived that the IRs for mortality of tofacitinib 5 mg fall within the same range as of other studies in patients with RA and at least one CVD risk factor.

3. Expert consultation

The PRAC consulted an ad-hoc expert group which provided advice on a number of issues.

VTE

Question 1

Preclinical signals suggest that in vivo JAK2 inhibition may occur at higher doses of tofacitinib. A slight decrease of platelet count has been observed in patients, which can be explained by JAK2 inhibition. Considering the differential effects of thrombopoetin on megakaryocytes (MK) progenitors and precursors in the early progenitor stage and on platelets (Skoda et al., 2014), a rebound effect on platelet count after substantial decrease of plasma concentrations or discontinuation of tofacitinib could be a potential mechanism contributing to the observed increased incidence of pulmonary embolism associated with the treatment with tofacitinib 10 mg. What is the opinion of the Ad-hoc expert group on this potential mechanism and its potential clinical relevance?

Based on the responses submitted by the MAH, this potential mechanism is less plausible. Hence, this question was not further pursued. Biomarker or plausible mechanism of action has yet to be identified in order to help in defining a population at high risk of thrombogenic events. A potential rebound effect on platelets might contribute to a small extent but has no real clinical significance.

Question 2

Could the risk of VTE be managed in the post-marketing setting with thromboprophylaxis?

The experts were of the opinion that patients with previous history of VTE should be maintained under thromboprophylactic treatment while treated with tofacinib, and should avoid oral contraception and other risk factors for VTE where possible. This recommendation would apply for UC, RA and PsA patients for both registered doses of tofacitinib (5mg and 10mg) and, for the 10mg dose, during the induction and the maintenance phase in UC. The experts also discussed which medicinal product or class would be best used in thromboprophylaxis. It was agreed that there is not enough data to support a specific recommendation and currently this should be left to the physician to make an individual judgment.

For primary prophylaxis the experts concluded that the benefit/risk is not established enough to justify thromboprophylaxis regardless risk factors.

Until the risk is better characterised, the experts expressed the view that the prescribers should be adequately informed of the risk of VTE in order to allow them to manage it appropriately.

As a general comment, the experts agreed that data available at present are limited and that the MAH should make every effort possible to better characterise the risk of VTE especially in high risk population e.g. in patients receiving tofacitinib 10mg BID treatment, women on oral contraceptives, smokers and patients with other identified risk factors.

Arthritis indications

Question 3

What is the opinion of the Ad-hoc expert group about the place of tofacitinib among other pharmacological treatment options for Rheumatoid Arthritis (RA)/Psoriatic Arthritis (PsA) in clinical practice?

Based on the evidence available at present, the experts were of the opinion that the current (EULAR, 2019) treatment recommendations for tofacitinib in patients with RA and PsA should apply and do not need modification. Accordingly, in clinical practice a physician might initiate treatment with a JAK inhibitor before a biologic agent in patient with much co-morbidity, taking advantage of the short half-life of tofacitinib.

The experts acknowledged that RA and PsA were different diseases and that the risk factors for VTE were different between the two diseases. However, the risk minimisation measures proposed in the response to question 2 would apply for both RA and PsA patients. The experts agreed that a cautious individual approach, especially in patients with increased risks of VTE, should be taken when prescribing tofacitinib. Further recommendations need to be developed when more data are available.

One patient representative expressed the view that there seems to be much uncertainty regarding the risk of VTE with tofacitinib treatment, in particular in PsA. Hence, a cautious approach with tofacitinib treatment should be applied until long term real world data are available.

Question 4

In the opinion of the Ad-hoc expert group, may patients with known VTE risk factors be treated with tofacitinib? Is there any specific RA/PsA population where tofacitinib should not be used?

The experts were of the opinion that patients with known VTE risk factors could be treated with tofacitinib provided that appropriate risk mitigation measures are put in place and taking individual cautious approach by treating physician as explained in answer to Question 2.

Based on the data available at present, the experts were of the opinion that there was no indication of a specific RA/PsA populations where tofacitinib should not be used.

Ulcerative colitis indication

Question 5

To what extent, could the results on the risk of venous thromboembolism in RA patients in study A3921133 be extrapolated to UC patients in routine clinical practice taking into account any differences in risk factors for venous thromboembolism with respect to the underlying condition and demographics of RA and UC patients?

Although the signal detected in the RA trial needs to be considered for UC population it is not clear if the results in the RA population can be directly extrapolated as the 2 populations are very different. UC and RA are different diseases and the baseline risk of thrombotic events in UC patients is naturally higher than in RA patients due to disease itself and different patients' characteristics.

No supportive evidence is available to assess the risk of VTE in UC patients treated with tofacitinib. However, acknowledging that the assessment of the risk of VTE in UC was made based on extrapolation from RA data, the experts were of the opinion that this risk could be similar in UC and RA patients.

Question 6

What is in the opinion of the Ad-hoc expert group the place of tofacitinib among other pharmacological treatment options for UC in clinical practice?

Based on the evidence available at present, the majority of experts were of the opinion that the current treatment recommendations for tofacitinib in patients with UC should not be modified. In patients with increased risk of VTE cautious individual approach should to be applied until risks are better determined to allow more general recommendations.

As discussed above, the risk minimisation measures based on individual clinical judgment proposed in the response to question 2 should apply for UC patients.

One expert agreed with the above; however, with the nuance that for patients with risk factors for VTE (including previous VTE event), other medical options should be considered over tofacitinib.

One expert expressed the divergent view that tofacitinib should only be used if other biologics fail in particular in patients with additional risk factors for VTE and that the use of 10 mg BID should be avoided over extended times (e.g. more than 8 weeks).

One patient representative mentioned that all UC treatments have side effects. Provided that there was a clear benefit with tofacitinib treatment, his view was that the risk of VTE would be acceptable to him.

Experts agreed that risks of other available treatments including steroids, immune suppressants, biologics or colectomy need to be taken into account when making individual treatment decisions.

Question 7

May patients with known VTE risk factors be treated with tofacitinib? Is there any specific UC population where tofacitinib 5mg BID or 10 mg BID should not be used or the use should be limited?

The majority of experts were of the opinion that patients with known VTE risk factors could be treated with tofacitinib 5mg BID or 10 mg BID both during the induction and the maintenance phase provided that appropriate risk minimisation measures - as proposed in the response to question 2 - are put in place.

As mentioned in the response to Question 6, one expert expressed a divergent view.

At present it is not possible to identify UC subgroups in which tofacitinib use should be limited. However, there was a consensus among experts that a cautious individual approach should be recommended. Some experts also underlined that for patients with risk factors for VTE (including previous VTE event), other medical options should be considered over tofacitinib as part of this individual cautious approach.

4. Benefit-risk balance

The efficacy of Xeljanz in its approved different indications has been previously established and is not questioned in the present procedure.

The available data shows that tofacitinib increases the risk of venous thromboembolism (DVT and PE) in patients with RA and PsA, especially in patients treated with tofacitinib 10 mg BID, and especially in patients with risk factors for venous thromboembolism, as well as risk factors for cardiovascular events. Data from patients suffering from UC although somehow limited do not indicate an increased risk of VTE in a population already with a baseline increased risk of thrombotic events. However, the risk of VTE appears to be higher in patients with UC in remission. As it is assumed that thrombotic events share a common mode of action the results drawn from the RA study (A3921133) can be - with some caution - extrapolated to other indications.

With regards to mortality (taking into account on-drug and the 28-days off-drug data), the interim analyses of Study 1133 indicate a borderline-significant increment of two times for the low tofacitinib dose, and significantly 3 times increment for the high dose, versus active control TNFi. This was partly driven by a higher mortality rate due to infections for tofacitinib. Mortality rates due to cardiac events were about twice as high for the 10 mg BID dose as compared to the active controls (TNFi), which cannot be explained by a raise in PE events. A higher mortality rate for 10 mg as compared to 5 mg is not apparent from other studies.

Rheumatoid arthritis and psoriatic arthritis

The PRAC concluded that the dose dependent risk of thrombotic events, although serious and potentially life-threatening, can be managed with the implementation of appropriate risk minimisation measures.

In Study 1133, the size of the risk of pulmonary embolism was on average modest for the low 5 mg BID dose (in contrast to the 10 mg dose arm), which is the standard dose for the arthritis indications (incidence rate 0.27 per 100 patient years (95% CI 0.12-0.52) additive risk 1.8 /1000 PY). Of note RA patients are already a population at risk for thrombotic events as compared to the general population. However, in presence of one or more risk factors for PE/DVT, there is evidence that the risk for PE/DVT is also raised for tofacitinib 5 mg BID as compared to anti-TNF.

Therefore, treatment with tofacitinib, in patients with additional risk factors for PE/DVT, should be carefully evaluated. As such PRAC considered that it should be emphasized in the SmPC that the recommended dose of 5 mg BID should not be exceeded for RA and PsA. After consultation with experts at an ad-hoc meeting, PRAC also concluded that the provisional contra-indication was not deemed necessary. Instead, the experts were of the opinion that patients with known VTE risk factors could still be treated with tofacitinib provided that appropriate risk mitigation measures are put in place and taking an individual cautious approach by the treating physician (including avoidance of oral contraception and other risk factors for VTE where possible).

The observed increased mortality in the preliminary analyses of Study 1133 is also of concern. However, the increased mortality is not reflected in the other non-1133 RA long term extension studies for the 5 mg and 10 mg dose. Patients were allowed to switch in those studies and as such the observed contrast/difference is smaller. Mortality is included as an outcome in the existing on-going PASS studies, which over time may provide further information about mortality of 5 mg tofacitinib as compared to other treatments.

The most frequently occurring death causes for the 5 mg, as compared to anti-TNF, were serious infections, whilst it was cardiovascular deaths for the 10mg dosage. A statement has been introduced in the SmPC in order to further highlight that the 10 mg dosage should not be used for RA and PsA.

The MAH was requested to evaluate whether patients at increased risk for death during treatment with tofacitinib could be identified. Although clear risk factors could not be identified, for patients around 65 years of age and above, the risk for mortality is increased. This increase was higher for tofacitinib as compared to anti-TNF, and was mainly attributable to serious infections. A warning has been included in the SmPC highlighting that tofacitinib should only be considered in patients over 65 years of age if no suitable alternative treatment is available and the educational materials was amended accordingly.

As mentioned above, although the risk of PE and mortality are considered very serious PRAC concluded that the risk can be appropriately managed with the inclusion of warnings for patients at increased risk for thrombotic events.

Ulcerative colitis

Inflammatory bowel disease itself is associated with an approximately two-fold increase [relative risk 2.20 (95% CI 1.83 – 2.65)] risk of VTE compared to a general population without inflammatory bowel disease[3]. Furthermore, VTE in UC patients is associated with considerable morbidity and mortality with higher rates of death from pulmonary embolism in IBD patients than in the general population[5],[6].

Neither PE nor DVT were observed upon tofacitinib 10 mg BID induction treatment in studies A3921094 and A3921095 in patients with moderately to severely active UC. However, venous thrombo-embolic events PE (n= 4 out of 1157) and DVT (n= 1 out of 1157) were observed upon prolonged treatment (i.e. 217 to 1149 days) with tofacitinib 10 mg BID in UC patients in remission. All respective patients had one or more risk factors for cardiovascular disease. Despite the limited number of observed VTE cases among UC patients treated with tofacitinib, it is noted that all cases of VTE occurred during tofacitinib maintenance treatment at tofacitinib dosages of 10 mg BID, while no VTE cases were observed at tofacitinib induction treatment at the same dosage. These results show that disease activity may be of relevance with respect to the evaluation of the risk of VTE in UC patients. Tofacitinib may reduce the absolute risk of VTE in patients with active UC by virtue of its anti-inflammatory properties. Due to the (almost) absence of inflammation in patients with UC in remission,

[5] Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008;103:2272–80.”
[6] Jess T, Gamborg M, Munkholm P, Sorensen TI. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol. 2007;102:609–17.

the anti-inflammatory properties of tofacitinib will not compensate for the thrombogenic potential of tofacitinib. This would explain why all VTE cases were observed during tofacitinib maintenance treatment for UC in remission.

Despite the limited data on the risk of VTE during tofacitinib maintenance treatment for UC as compared to RA, it is plausible that tofacitinib may increase the risk of VTE in UC patients as was shown in RA patients, as it is unlikely that the safety profile of the active substance tofacitinib itself is substantially different for different indications. Therefore the above mentioned warnings are also relevant in this indication.

In patients who are at increased risk of venous thromboembolic events (e.g. obesity, advanced age, history of VTE) maintenance treatment with tofacitinib 10 mg is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available. A warning has been included in the product information accordingly. Further treatment with the 10 mg dose should be as short as possible in these patients.

In summary, the available data does not allow definitive conclusions with respect to the risk of VTE in UC patients treated with tofacitinib as compared to tofacitinib-treated RA patients. However, in RA patients a dose-dependent increase in VTEs and serious infections was shown upon tofacitinib treatment. It is plausible that similar effects may occur in UC patients. The tofacitinib related risk of VTE appears to be higher in patients with no active disease, i.e. disease in remission. It is unknown to what extent observations with respect to the VTE risk in RA patients seen in 1113 study may be extrapolated to UC patients. Nevertheless, the benefit/risk balance of tofacitinib in the treatment of UC remains positive. In patients with known risk factors for VTE, treatment with tofacitinib should be used with caution regardless of indication and dosage. In addition, tofacitinib 10 mg BID maintenance treatment should be prescribed for the shortest duration possible based on a careful weighing of benefits and risks in individual patients.

5. Risk management

5.1. Pharmacovigilance activities

5.1.1. Risk management plan

All available data, including data on the pathophysiology of the events (considering that PE is a special case of DVT) as well as the association of thromboembolism that has been identified in patients with other JAK inhibitors, have been considered. Therefore, and as requested by PRAC, the MAH included "venous thromboembolic events (DVT/PE)" as an important identified risk in the summary of safety concerns and all-cause mortality as an important potential risk in the summary of safety concerns. These important risks will be further characterised with the planned registry studies in all indications.

5.1.2. Non-clinical studies

The study "Biospecimen Testing Study" has been added as additional pharmacovigilance activity in the Risk Management Plan (category 3 study). It is a nested case-control biomarker study from the A3921133 open-label safety endpoint study in RA subjects with the aim to assess the biological basis for the observed excess risk of VTE in subjects receiving tofacitinib (10mg) and/or to identify patients at higher risk for PE or VTE events. The final report is expected in September 2020.

5.1.3. Clinical trials

Study 1133 is still ongoing for the tofacitinib 5 mg twice daily arm and TNF-inhibitors in RA patients; the final study report is expected in May 2022 and will be submitted to the PRAC. This study is included in the RMP as a category 3 study.

The long-term extension study in PsA (A3921092) to evaluate the long-term safety, tolerability, and efficacy of treatment with tofacitinib (5 mg BID and 10 mg BID) has been added to the RMP as a category 3 study. Venous thromboembolism (DVT/PE) and all-cause mortality are concerns addressed in this study.

5.1.4. Non- interventional studies

For the Ulcerative Colitis indication, Corrona (US database), the SWIBREG (Swedish UC registry study), UR-CARE (European UC registry study) and UC active surveillance study in the US (study A3921347) are planned. Venous thromboembolism (DVT/PE) and all-cause mortality have been included as safety concerns to be investigated within all registries (except from OTIS, which has the aim of estimating adverse pregnancy outcomes). Venous thromboembolism (DVT/PE) is a safety outcome for UC active surveillance study in the US, together with malignancies, opportunistic and serious infections, herpes zoster, major adverse cardiovascular endpoints, and gastrointestinal perforations, but not mortality. All-cause mortality should be included as addressed safety endpoint in the study A3921347.

The MAH should include updated study protocols for all the ongoing studies, and for all the planned studies in the Annex 3 of the RMP reflecting the risk of VTE and mortality in the study objectives. This should be done within the next regulatory procedure involving the RMP. It should also be reflected in the RMP that safety outcomes with 10mg BID during maintenance therapy will be evaluated in a separate sub-analysis.

Two prescribers' surveys (one RA indication and PsA and another in UC indication) and a Drug Utilisation Study to be conducted in EU databases are planned in order to monitor the effectiveness of RMM of updated measures.

The prescriber surveys aim to study HCP knowledge and adherence to the warnings and recommendations for tofacitinib. The MAH proposed two separate surveys (one among RA prescribers and the other among PsA/UC prescribers) for which different timelines have been suggested, with RA survey being planned shortly. However, considering important updated recommendation in the SmPC that are also relevant for RA prescribers, the PRAC considered that the planned survey in RA indication should not be performed now and that the questionnaire needs to be updated in line with the newly implemented recommendations regarding the risk of VTE and mortality. To this end, the MAH should conduct one HCP survey among the prescribers for all indications i.e. rheumatologists and gastroenterologists. This survey should be performed 6-9 months after implementation of the updated aRMM. With this approach, all data regarding HCP knowledge and adherence on the current aRMMs and updated recommendations regarding VTE will be studied among all type of prescribers and will become available at the same time. The survey may include different/additional questions for the UC prescribers compared to RA/PsA prescribers.

The study protocol of the HCP survey in the RA/PsA/UC indication, in line with the already approved RA HCP survey study protocol and taking into account the new prescribing recommendations in the PI, should be submitted for assessment following the outcome of the current referral and within 3 months after EC decision. The planned date for the survey start is December 2020.

The EU DUS (A3921321) across all indications, using electronic healthcare databases, will study how the 5 mg BID and 10 mg BID are utilised in clinical practice and will study compliance to patient

monitoring before and during tofacitinib treatment (i.e. infections, malignancy, liver function test and laboratory parameters such as lymphocytes, neutrophils, haemoglobin, lipid monitoring) as well as compliance to the updated recommendations regarding limitations of use (including off label use of 10 mg BID among RA/PsA patients, avoid use of 10 mg maintenance therapy among UC patients at high risk for PE or who are bDMARD naïve). The MAH should also evaluate the HCPs' compliance with the new recommendations to minimise the risk of VTE among all indications, i.e. tofacitinib should be used with caution in patients with known VTE risk factors regardless of indication and dosage, with a special focus on use of 10mg BID in UC patients for maintenance. The MAH should submit the study protocol within 3 months after finalisation of this referral procedure.

For the RA and PsA indications, the risk of venous thromboembolic events (DVT and PE) and mortality risk will be further characterised with the already planned registry studies in EU and US from the following databases: Corrona (US databases for RA and UC), ARTIS, BSRBR, RABBIT, and BIOBADASER (EU RA registries). VTE and mortality are already included in the study protocols of these registry studies and all tofacitinib users (both 5mg BID and 10mg BID if available) will be included in the analysis.

5.2. Risk minimisation activities

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risks associated with the use of Xeljanz. These changes include amendments to sections 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC.

The Package Leaflet was amended accordingly.

5.2.2. Direct Healthcare Professional Communications/Communication plan

The PRAC adopted the wording of a DHPC, to inform Healthcare Professionals of the outcome of the review including the updated of risk minimisation measures. The PRAC also agreed on a communication plan.

5.2.3. Educational materials

Additional risk minimisation measures (physician and patient educational materials) are already in place to address the risks of serious infections, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities. The key elements of both the physician (i.e. HCP guide and prescriber checklist) and patient educational materials with information on venous thromboembolic events (DVT and PE) will be update as follows:

- The signs and symptoms of venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]) will be specified in the material for the patient.
- Addition in the HCP checklist the recommendation that the prescriber should discuss with the patients the risks associated with the use of XELJANZ, including venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]).

Furthermore, for the educational material for HCPs the recommendation that tofacitinib should be used with caution in patients with known VTE risk factors and that 10mg BID is not recommended for

maintenance treatment in UC patients with known VTE risk factors unless there is no suitable alternative treatment available should be specified. Also the educational material needs to be updated with a warning for serious infections in elderly.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Xeljanz (tofacitinib).
- PRAC considered the totality of the data submitted during the referral in relation to the risk of venous thromboembolism and overall mortality, including the responses submitted by the marketing authorisation holder in writing as well as the outcome of a consultation with an Ad-hoc expert group meeting.
- PRAC concluded that tofacitinib is associated with an increased risk of venous thromboembolic events (VTE), both for deep venous thrombosis as well as pulmonary embolism, especially in patients with risk factors for venous thromboembolism. The PRAC further concluded that the risk of venous thromboembolism events is dose-dependent.
- PRAC concluded that although the data for patients with ulcerative colitis and psoriatic arthritis are limited, the results from study A3921133 in rheumatoid arthritis patients are relevant for the other indications.
- Based on the interim analyses of Study A3921133 the PRAC also concluded that there is a potential risk regarding increased mortality. This was partly driven by a higher mortality rate due to serious infections for tofacitinib. This was particularly apparent for patients aged 65 years and above and as such tofacitinib should be considered in these patients only if no suitable alternative treatment is available.
- To minimise these risks, PRAC recommended warnings to be introduced in the product information regarding the increased risk of VTE observed in patients taking tofacitinib especially for patients with known risk factors for VTE. The PRAC also recommended that treatment with tofacitinib is discontinued in patients with suspected VTE.
- Furthermore, PRAC introduced a warning that tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available. Clarifications on the posology have also been added particularly for UC patients in maintenance.
- PRAC recommended an update of the educational materials accordingly.
- PRAC also agreed on a direct healthcare professional communication, together with the timelines for its distribution.

In view of the above, the Committee considers that the benefit-risk balance of Xeljanz (tofactinib) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Xeljanz (tofacitinib).